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United States Patent [19]

Edwards et al.

[11] **Patent Number: 6,071,280**

[45] **Date of Patent: *Jun. 6, 2000**

[54] **MULTIPLE ELECTRODE ABLATION APPARATUS**

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[73] Assignee: **Rita Medical Systems, Inc.**, Mountain View, Calif.

[*] Notice: This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).
This patent is subject to a terminal disclaimer.

[21] Appl. No.: **08/802,195**

[22] Filed: **Feb. 14, 1997**

Related U.S. Application Data

[63] Continuation-in-part of application No. 08/515,379, Aug. 15, 1995, Pat. No. 5,683,384, which is a continuation-in-part of application No. 08/290,031, Aug. 12, 1994, Pat. No. 5,536,267, which is a continuation-in-part of application No. 08/148,439, Nov. 8, 1993, Pat. No. 5,458,597.

[51] **Int. Cl.**[7] **A61B 18/18**

[52] **U.S. Cl.** **606/41**; 607/101

[58] **Field of Search** 606/41, 42, 45–50; 607/100–102, 122, 154, 156; 600/372–374

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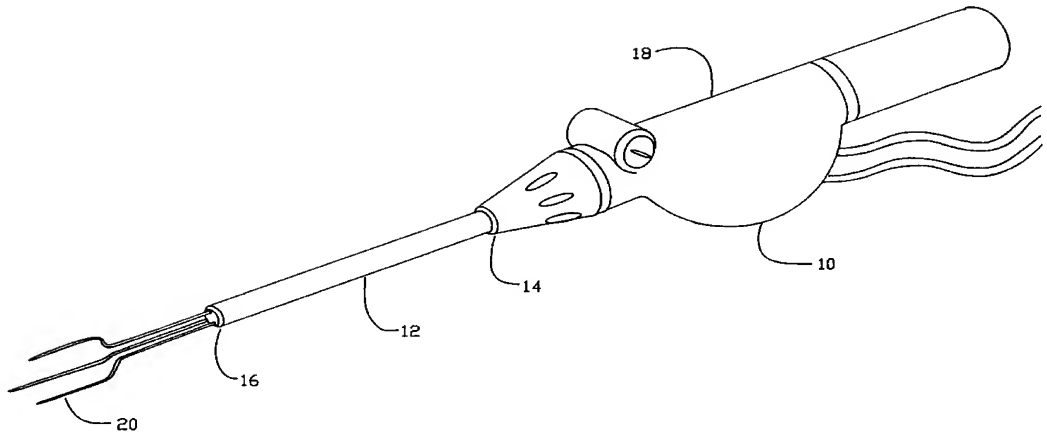
Primary Examiner—Michael Peffley
Attorney, Agent, or Firm—Wilson, Sonsini, Goodrich & Rosati

[57] **ABSTRACT**

A tissue ablation apparatus includes a delivery catheter with distal and proximal ends. A handle is attached to the proximal end of the delivery catheter. At least partially positioned in the delivery catheter is an electrode deployment device. The electrode deployment devices includes a plurality of retractable electrodes. Each electrode has a non-deployed state when it is positioned in the delivery catheter. Additionally, each electrode has a distended deployed state when it is advanced out of the delivery catheter distal end. The deployed electrodes define an ablation volume. Each deployed electrode has a first section with a first radius of curvature. The first section is located near the distal end of the delivery catheter. A second section of the deployed electrode extends beyond the first section, ad has a second radius of curvature, or a substantially linear geometry.

46 Claims, 21 Drawing Sheets



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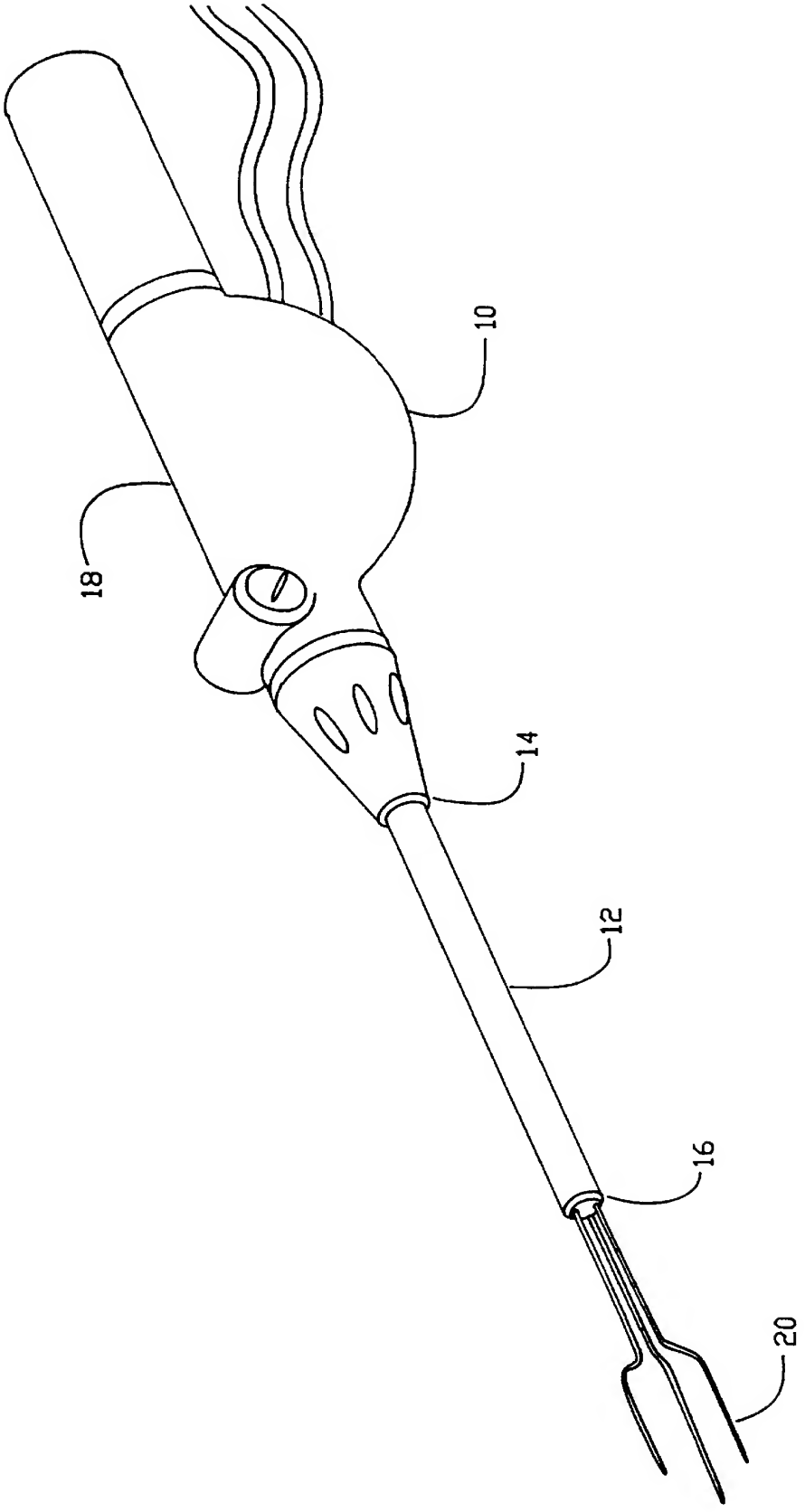


FIG. 1

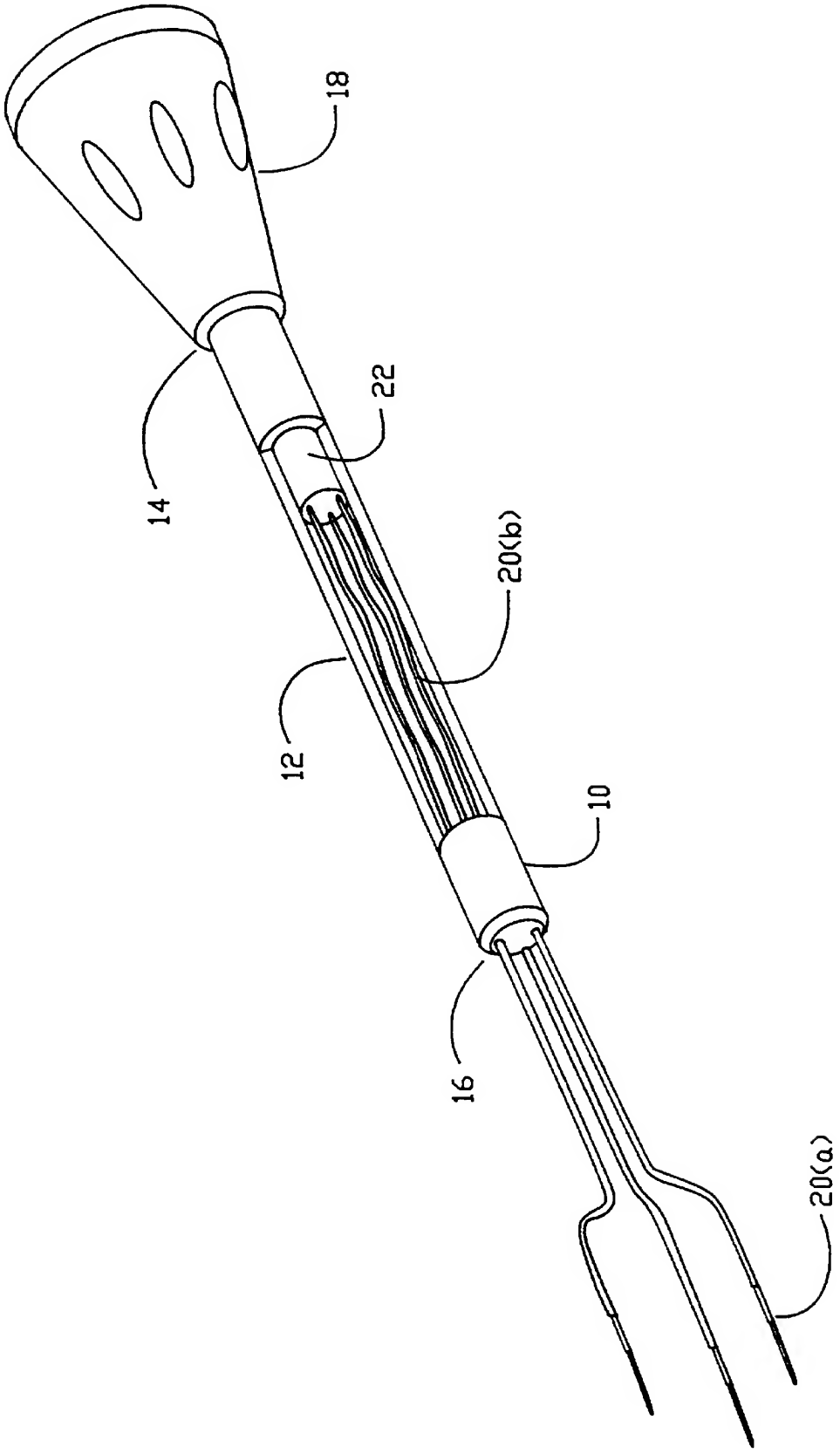


FIG.2

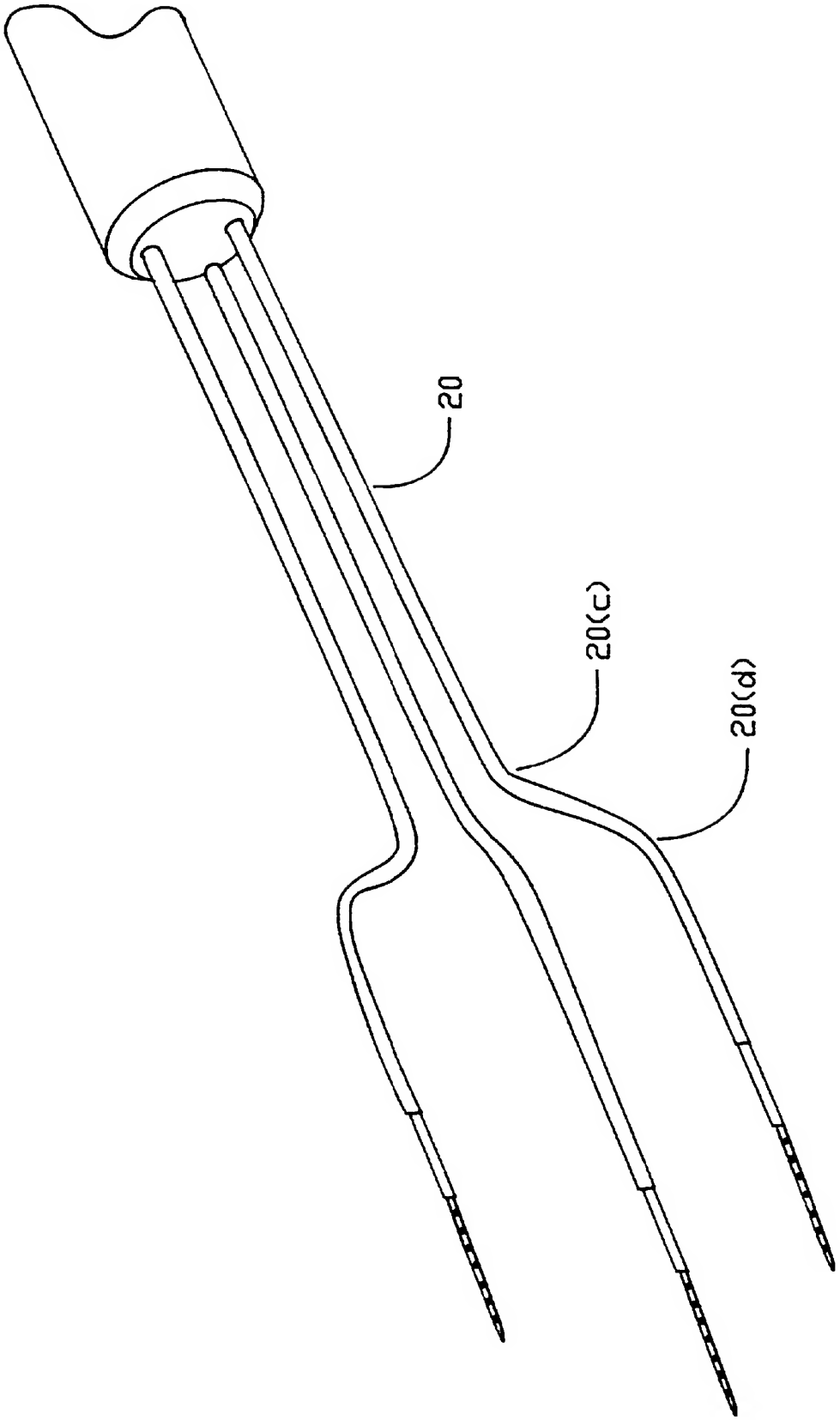
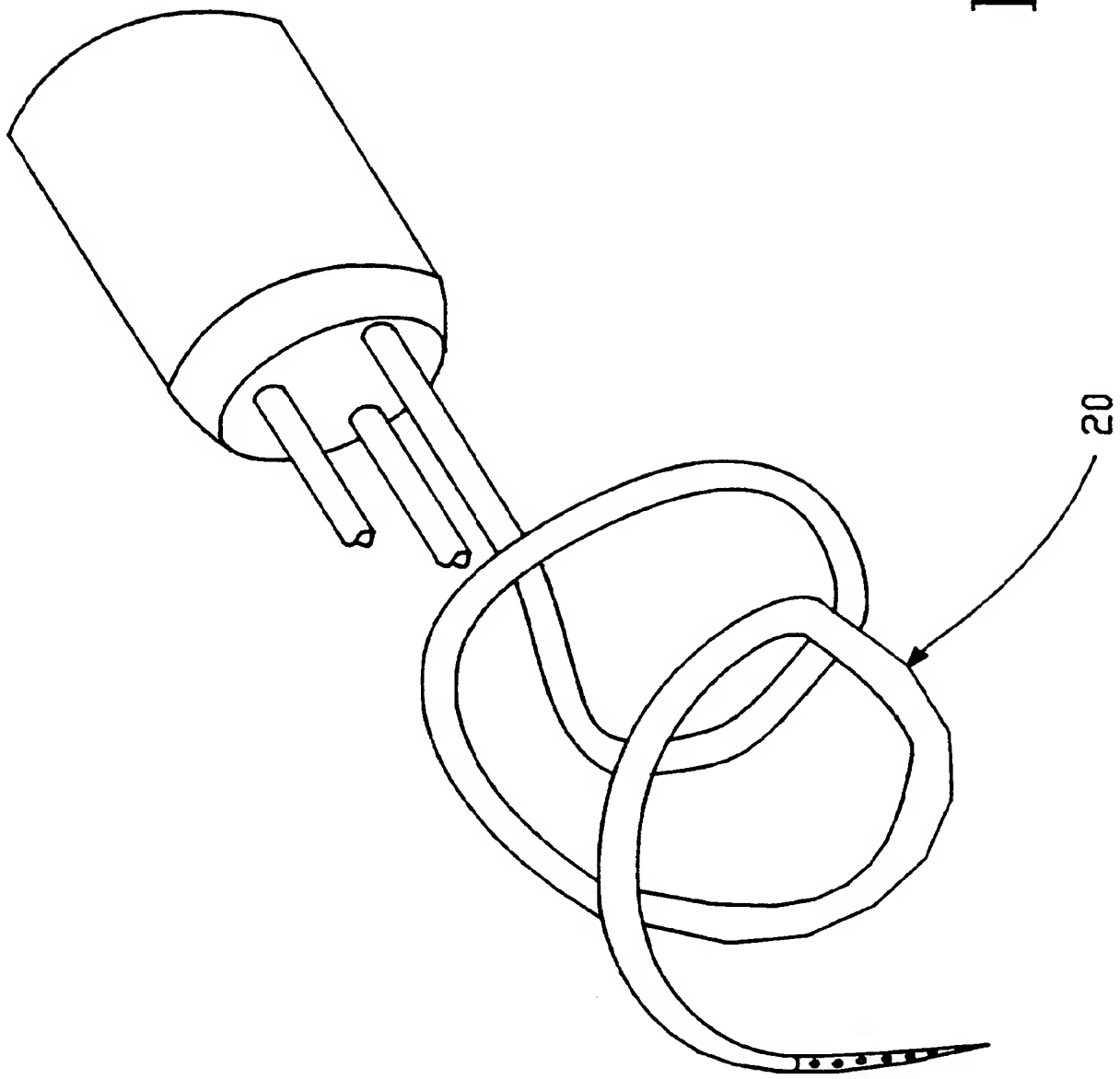


FIG.3

FIG. 4



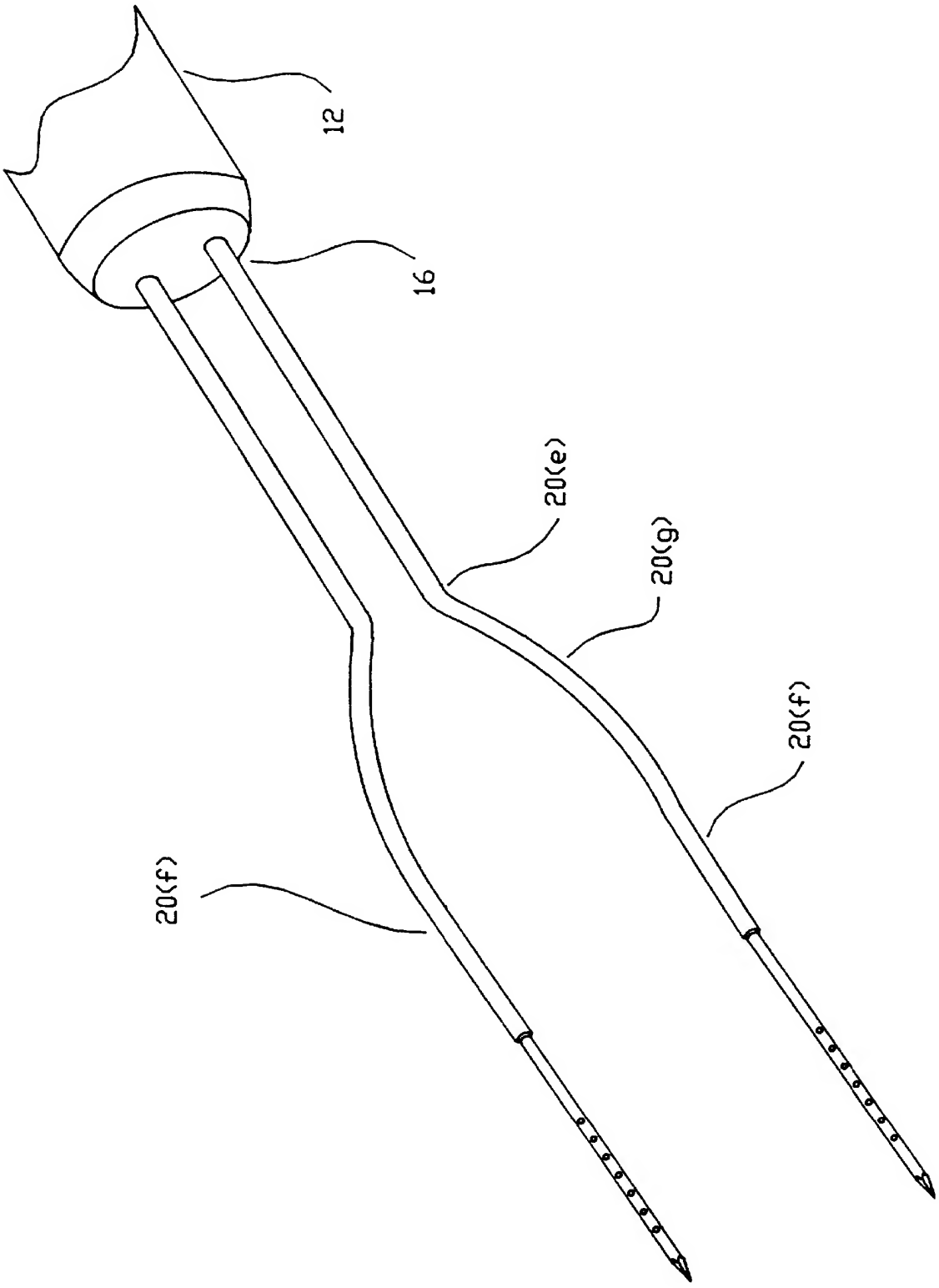


FIG.5

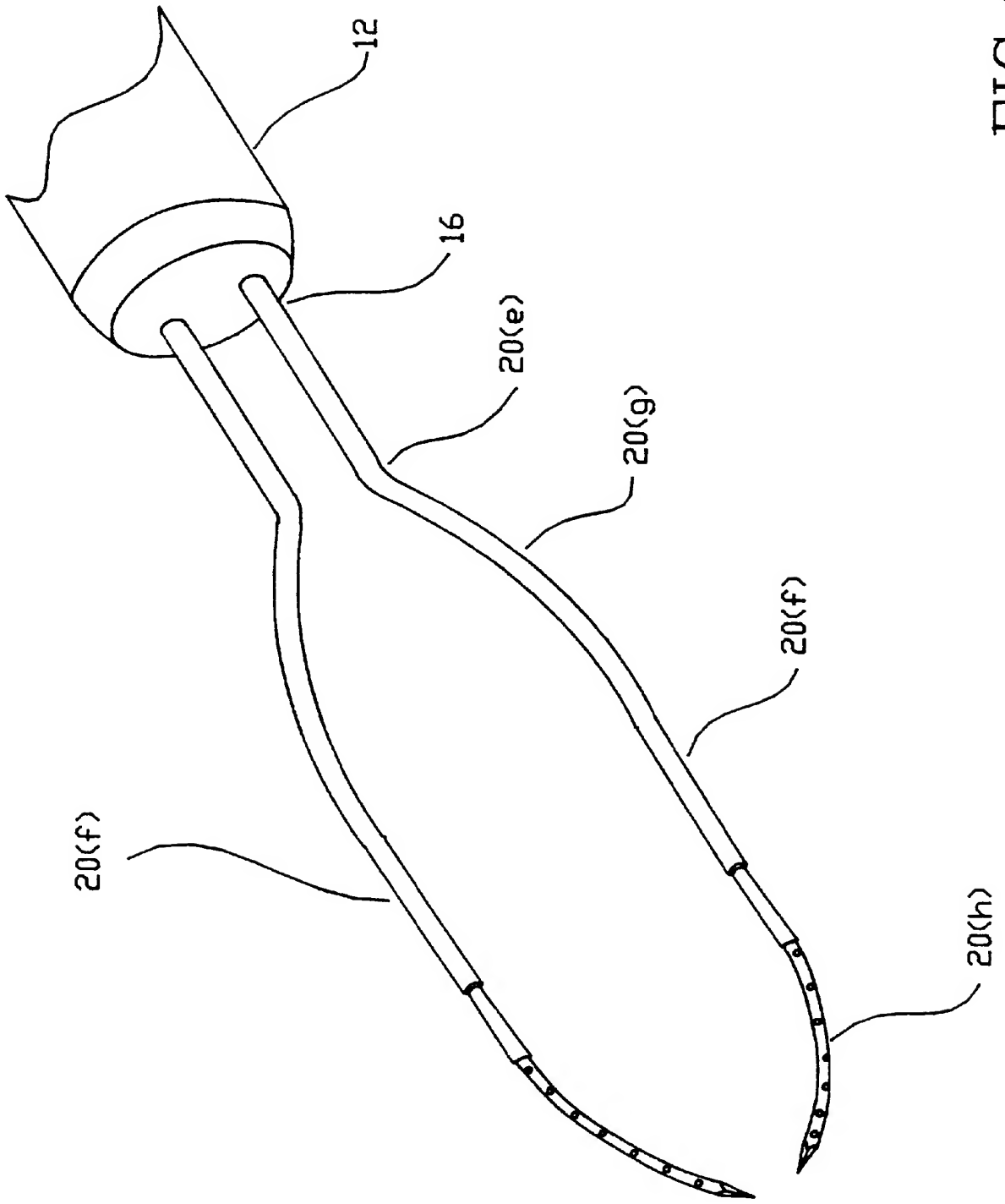
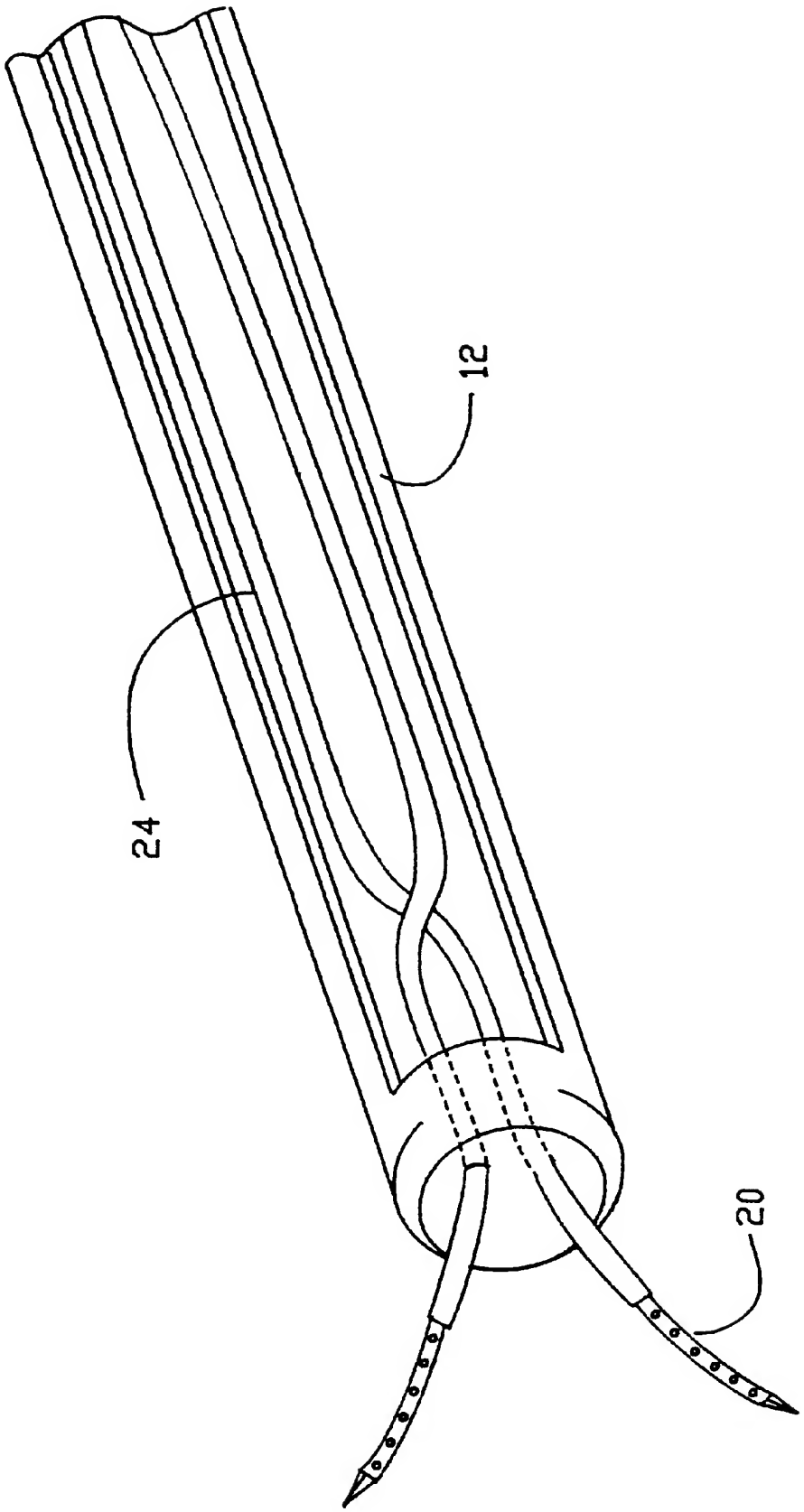


FIG.6



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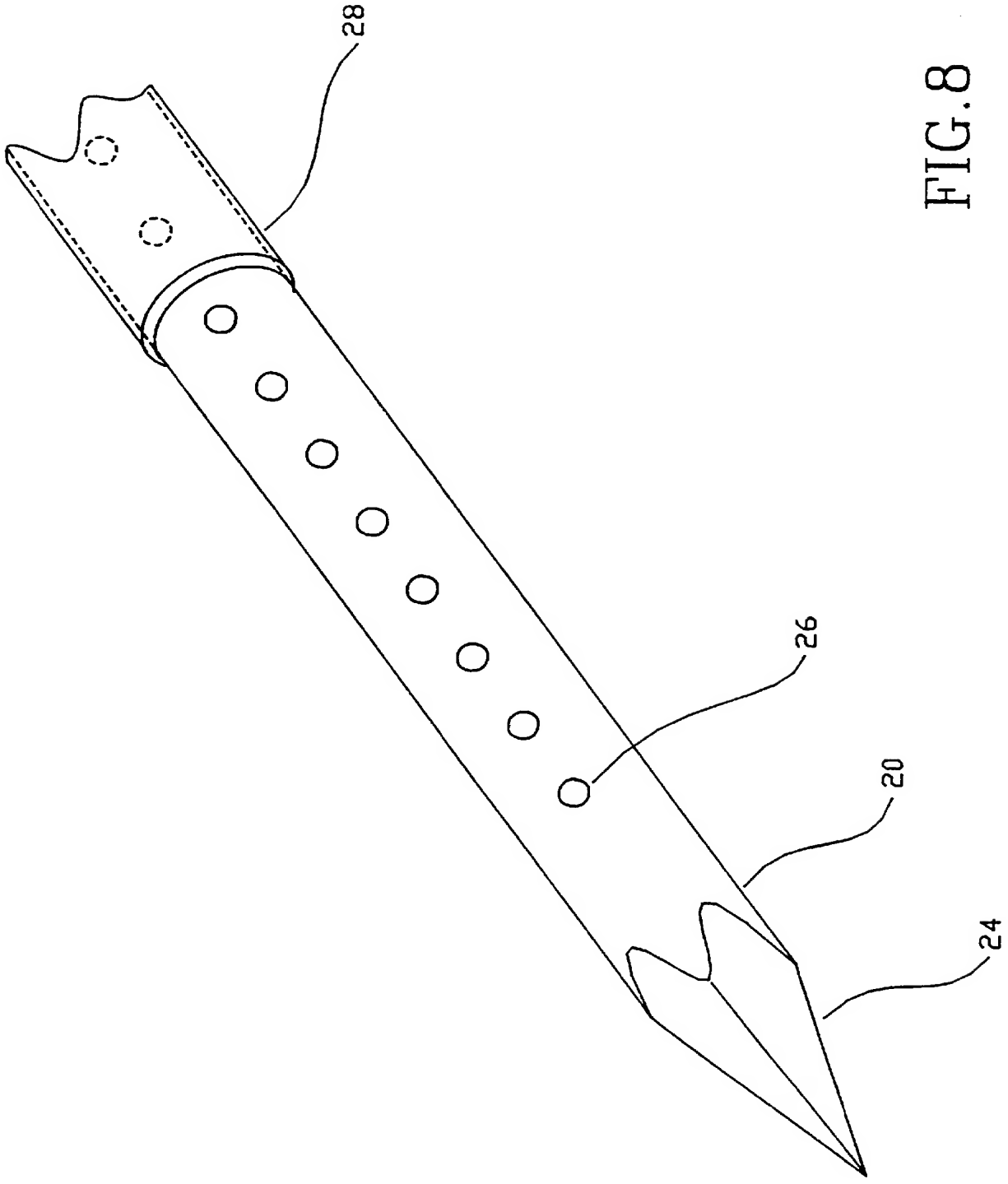


FIG.8

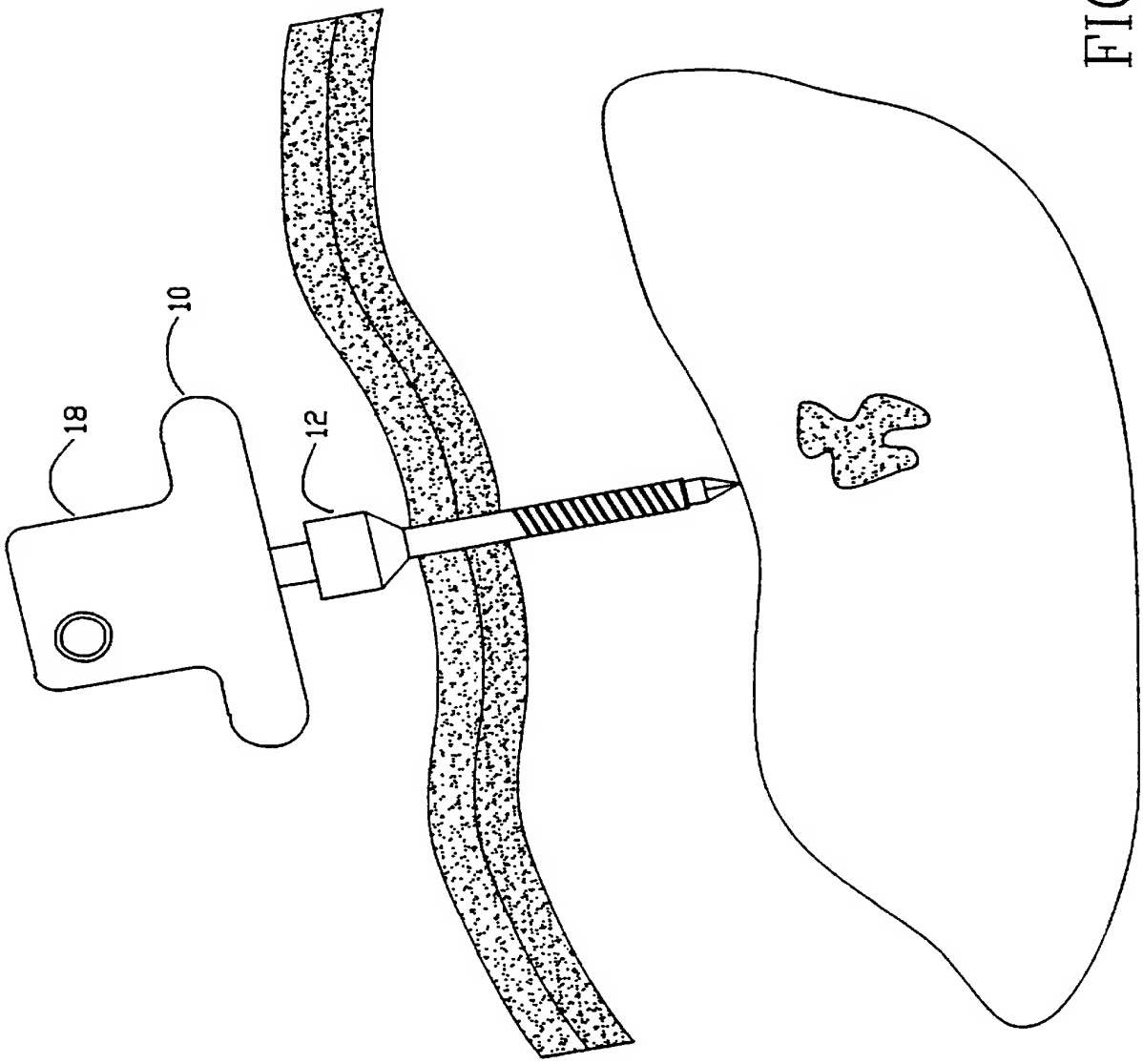


FIG.9

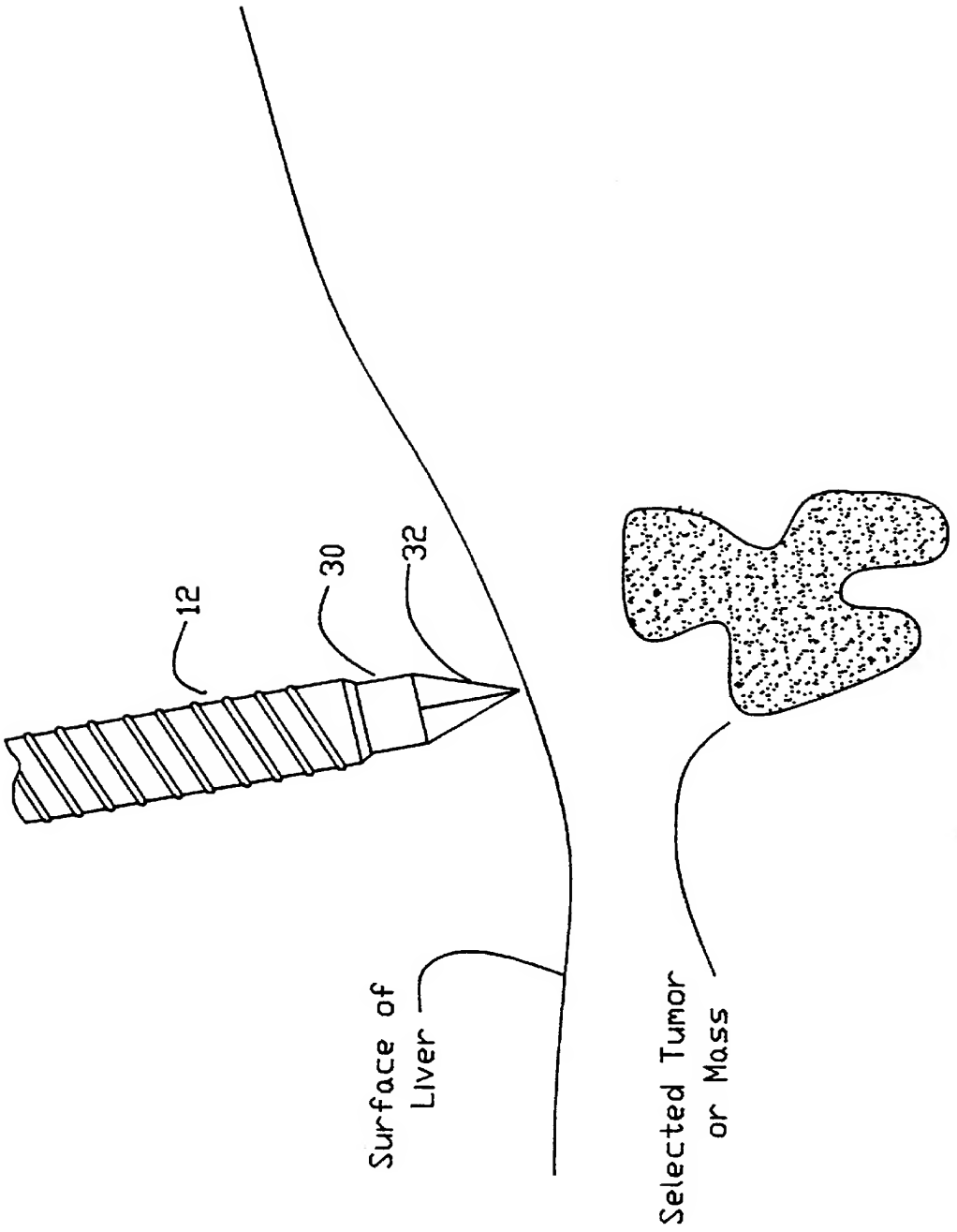


FIG. 10

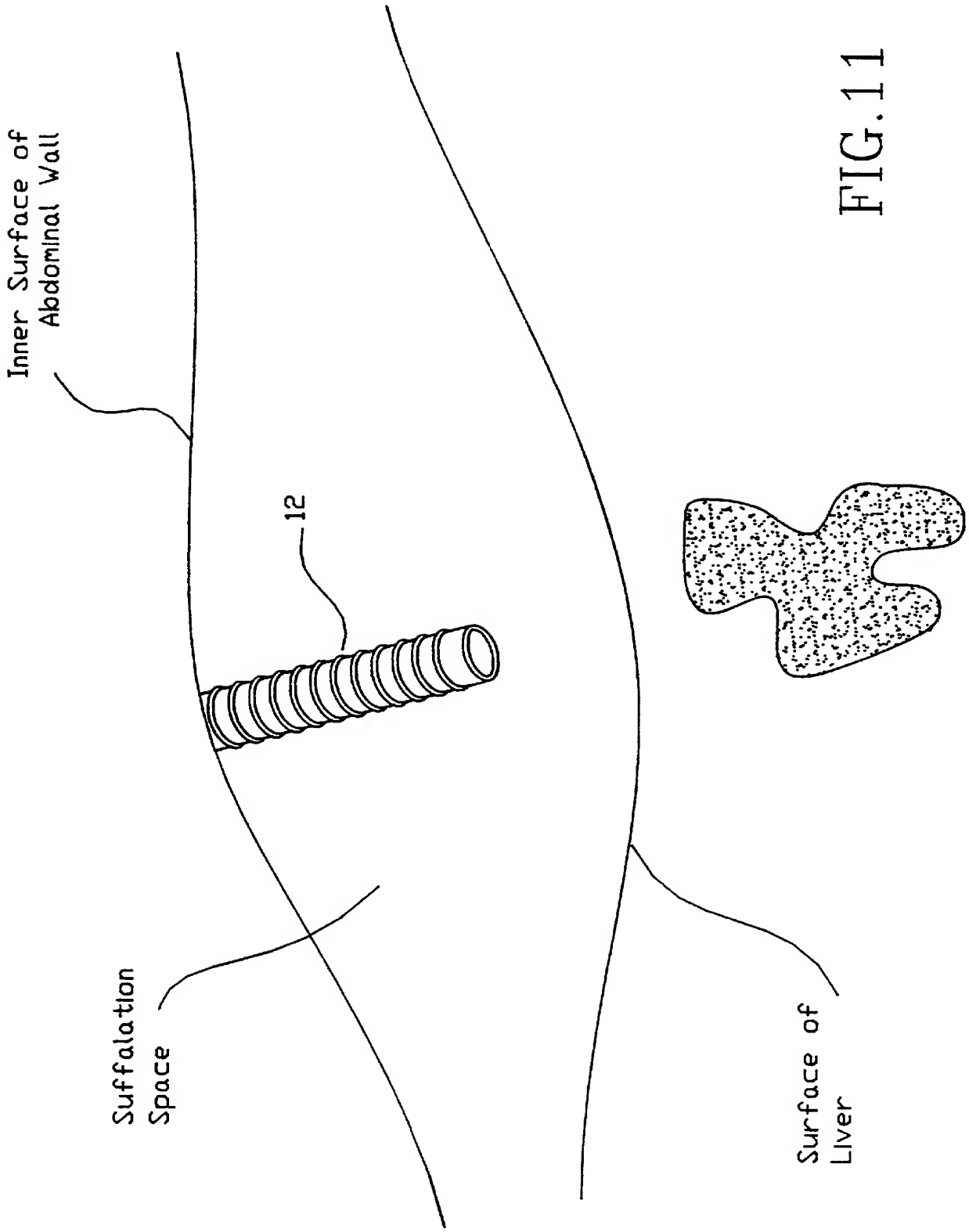
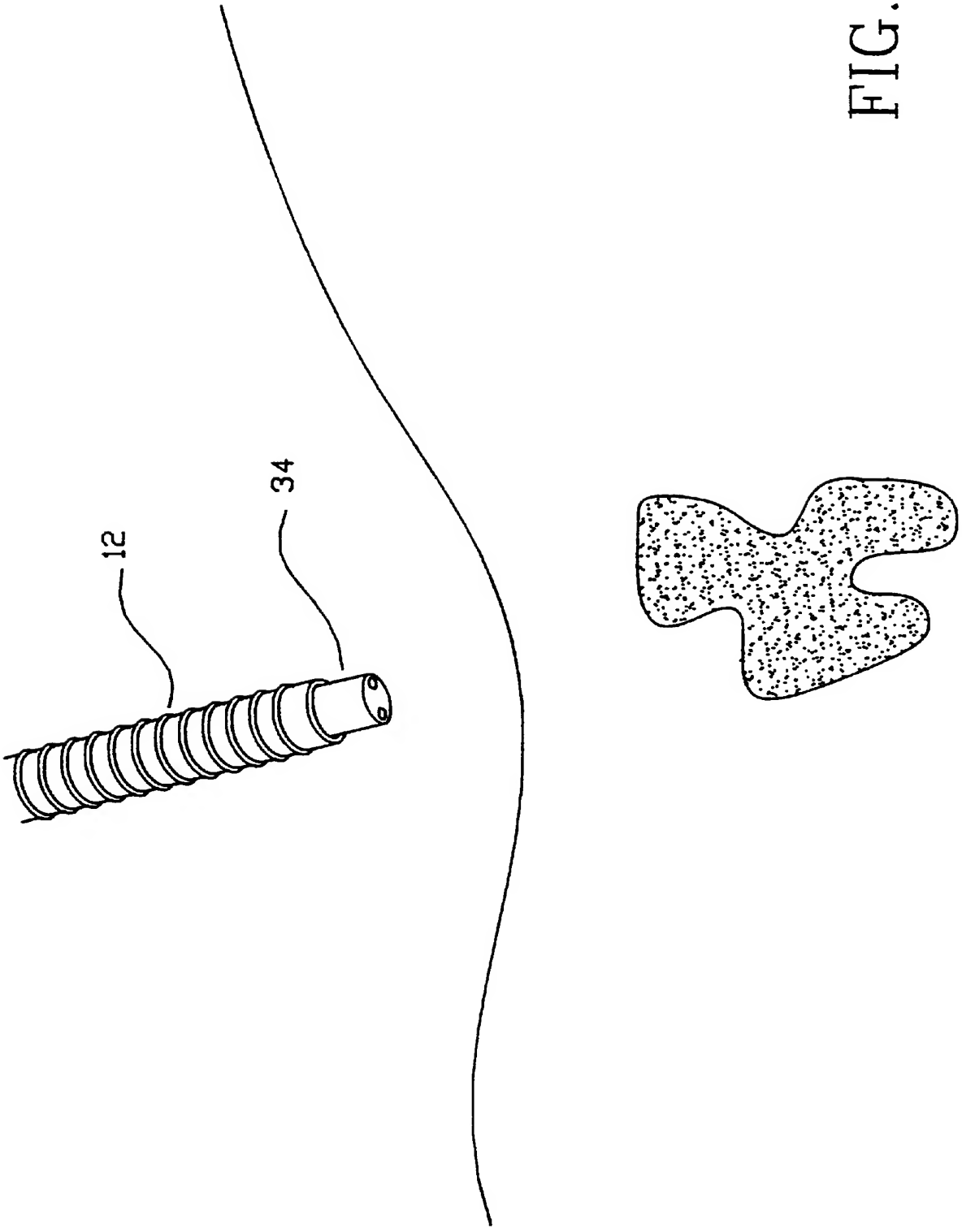

Inner Surface of Abdominal Wall
12
Suffalation Space
Surface of Liver

FIG. 11

FIG. 12



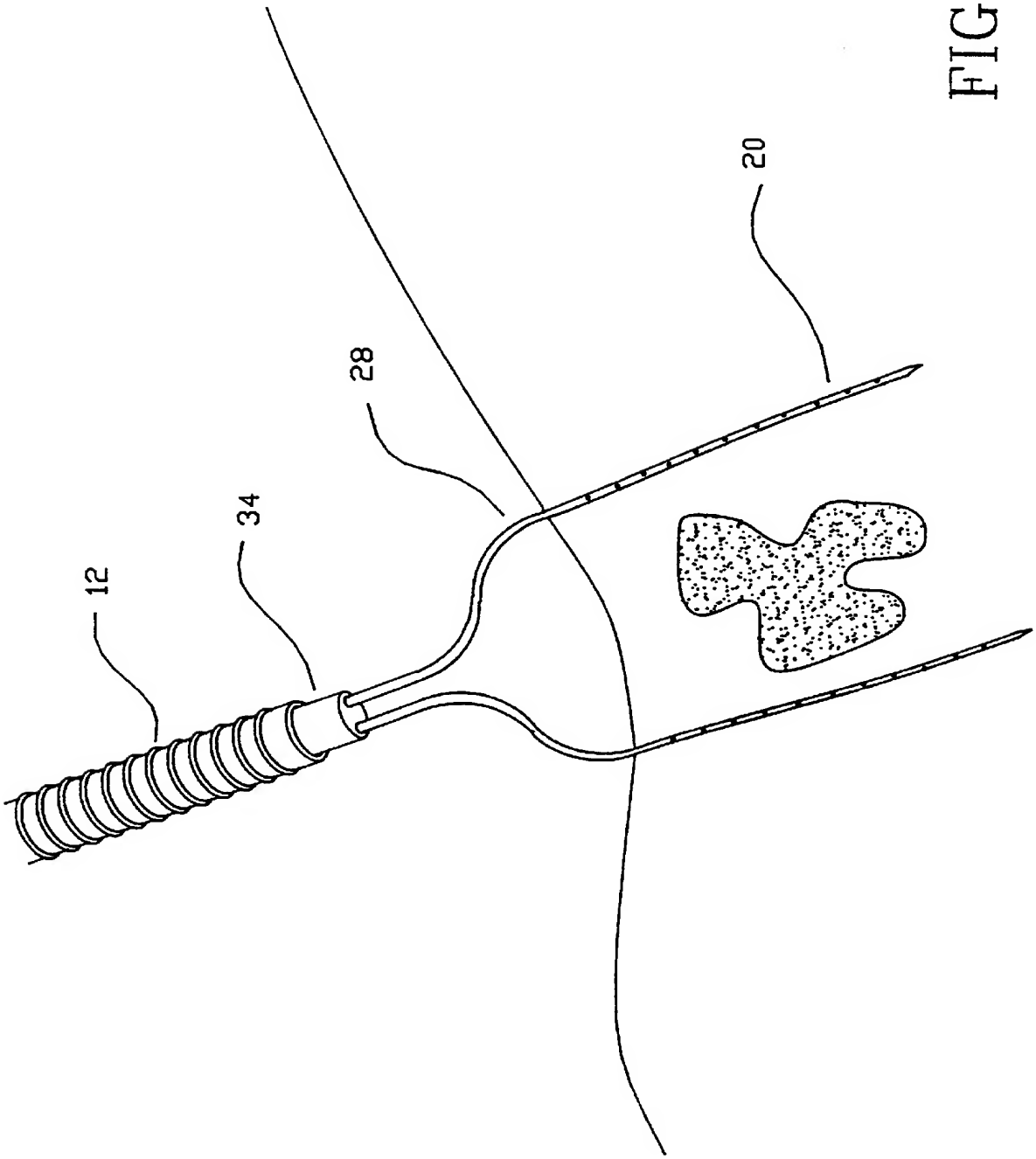


FIG. 13

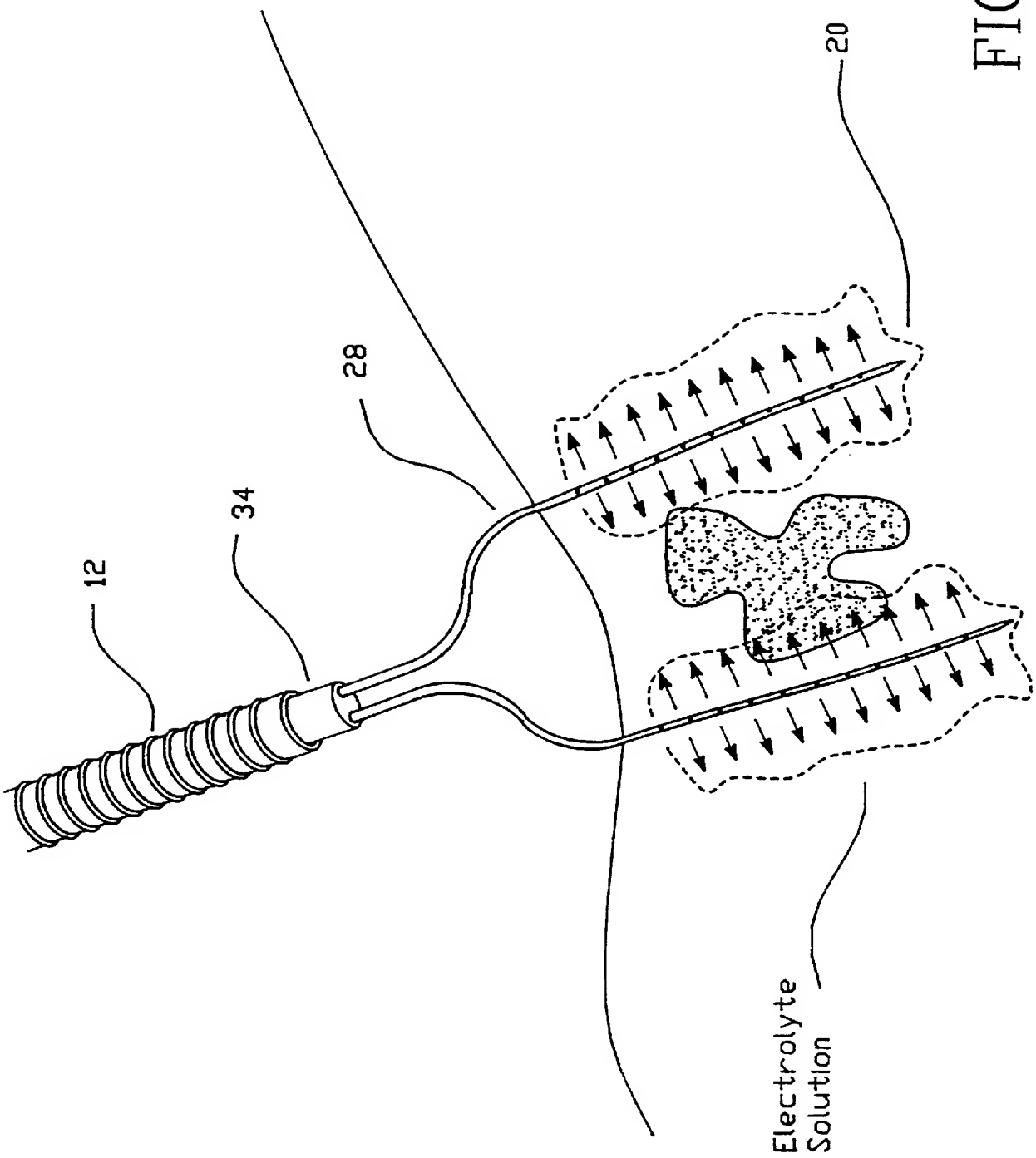


FIG. 14

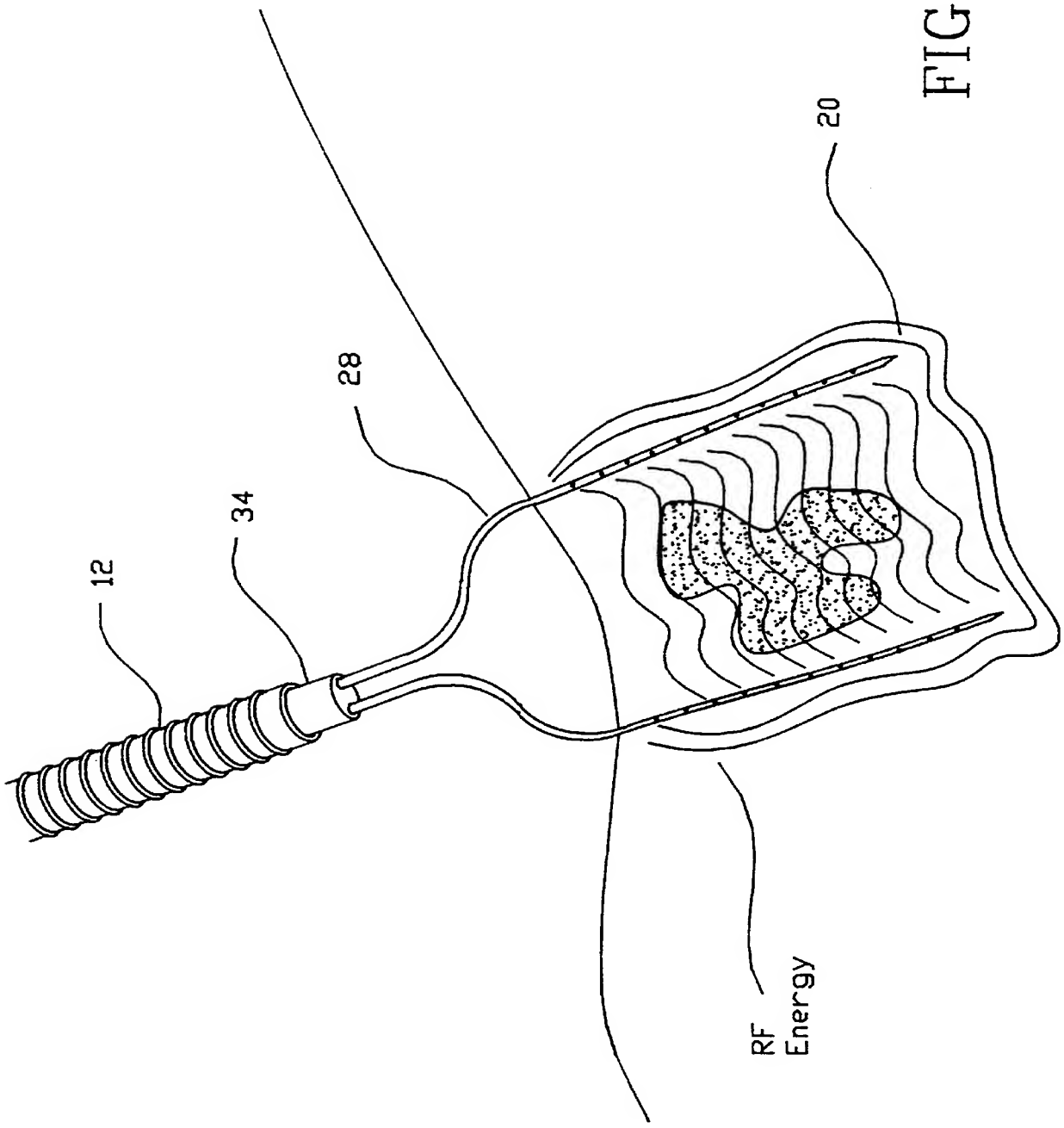


FIG.15

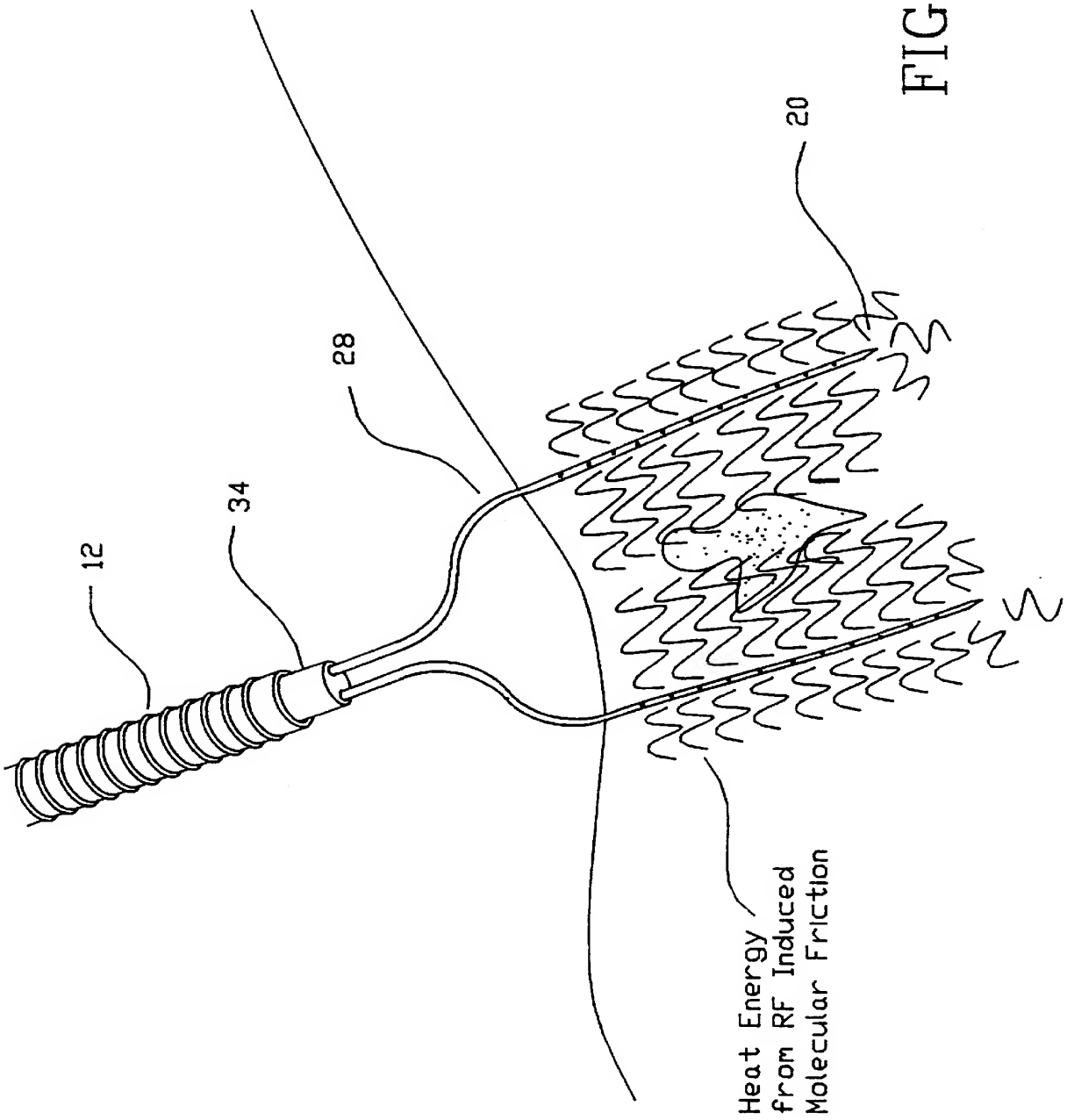


FIG. 16

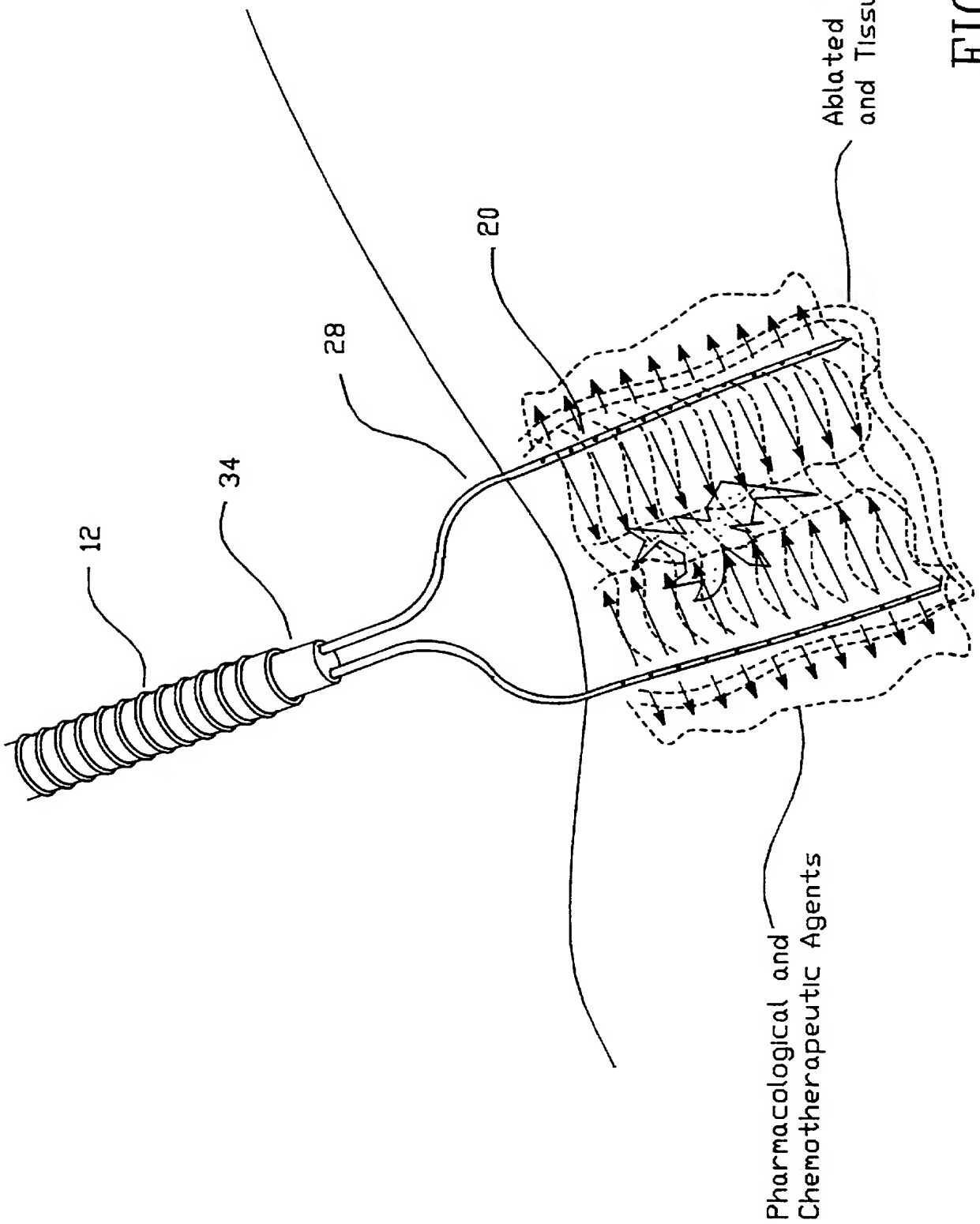

Ablated Tumor and Tissue
20
28
34
12
Pharmacological and Chemotherapeutic Agents

FIG. 17

FIG. 18

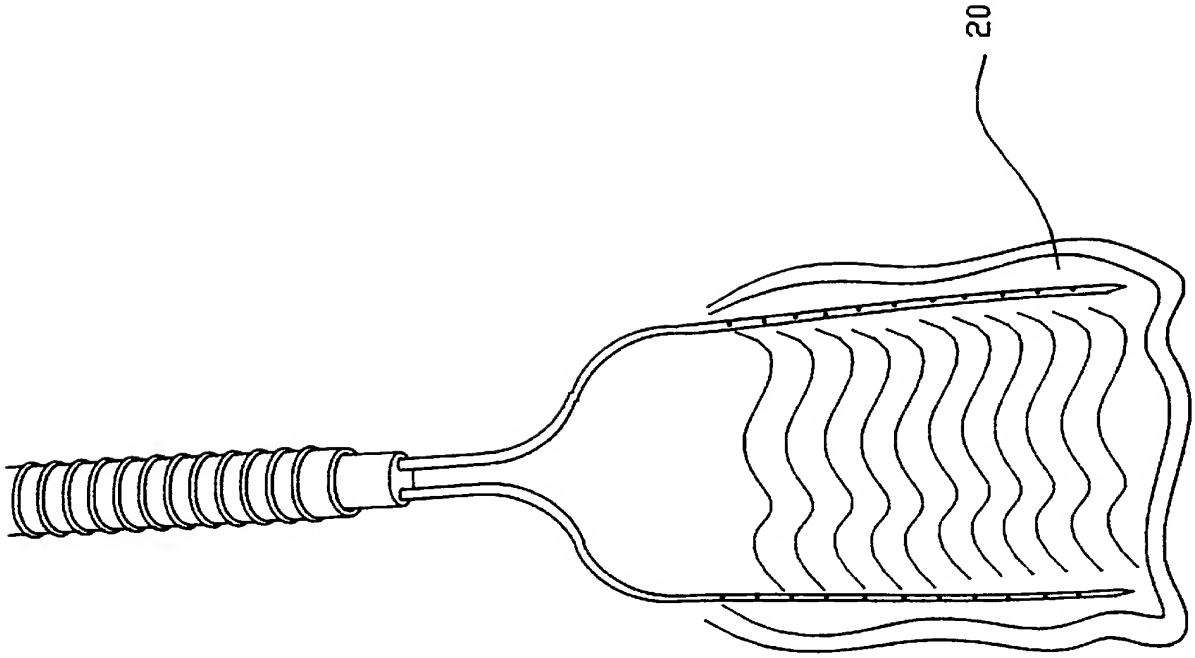
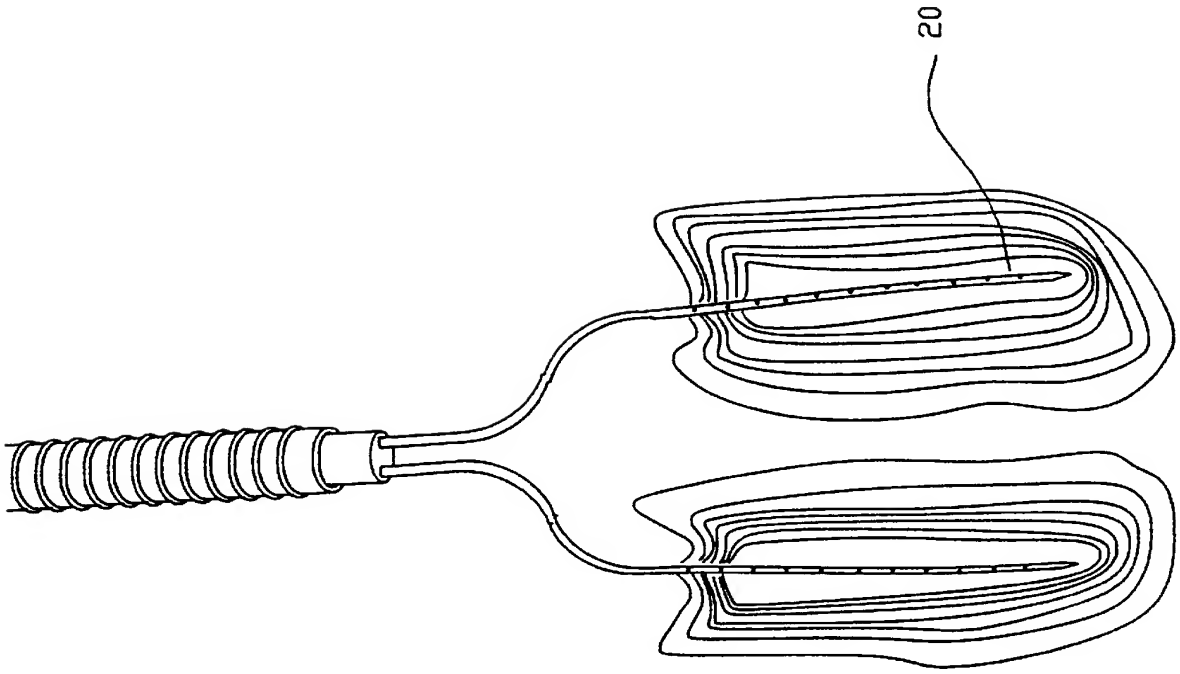


FIG. 19



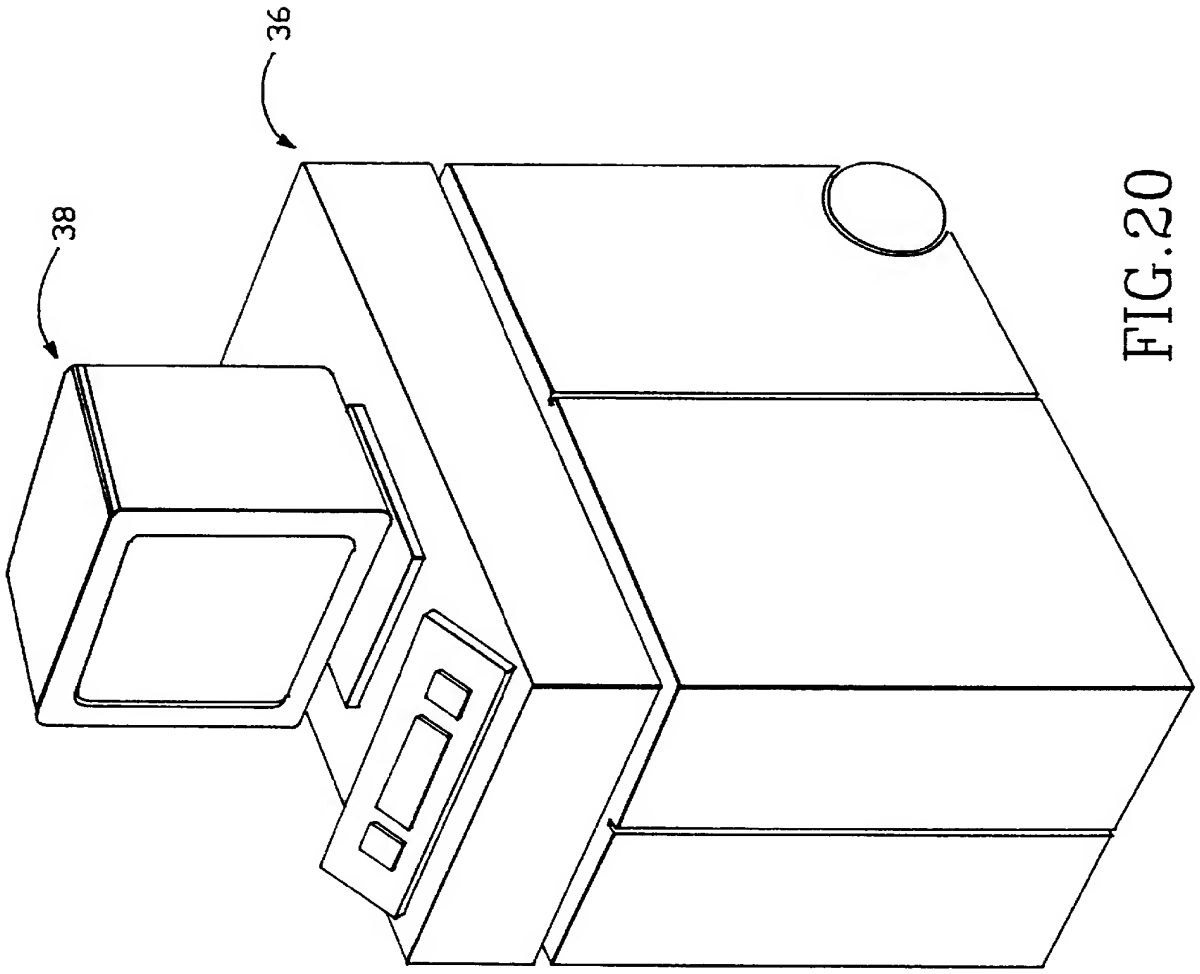


FIG.20

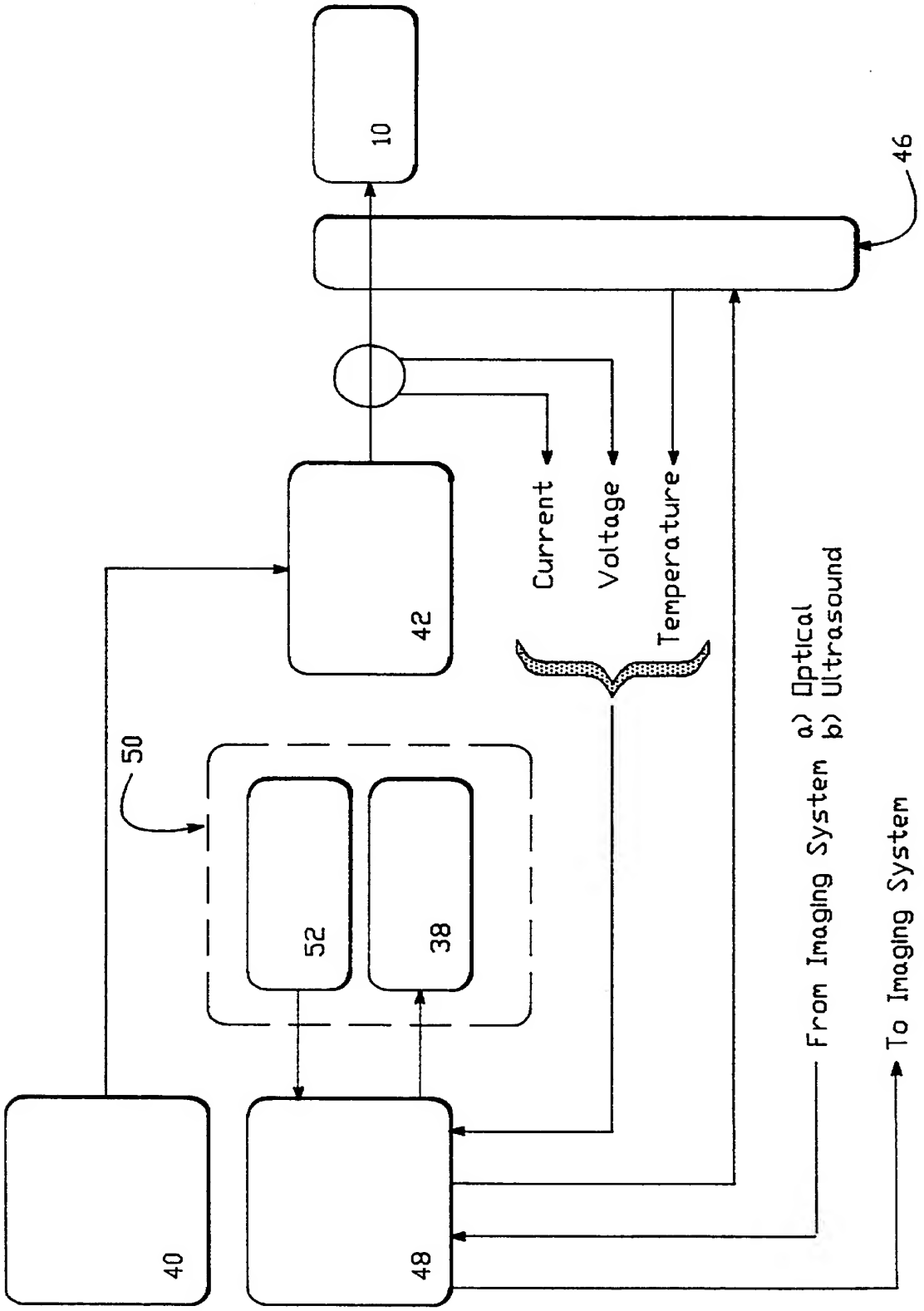

10
46
42
Current
Voltage
Temperature
50
52
38
40
48
a) Optical
b) Ultrasound
From Imaging System
To Imaging System

FIG.21

MULTIPLE ELECTRODE ABLATION APPARATUS

CONTINUING APPLICATION DATA

This application is a continuation-in-part of U.S. Ser. No. 08/515,379, filed Aug. 15, 1995, now U.S. Pat. No. 5,683,384, entitled MULTIPLE ELECTRODE ABLATION APPARATUS, which is a continuation-in-part of U.S. Ser. No. 08/290,031 Aug. 12, 1994 now U.S. Pat. No. 5,536,267, issued Jul. 7, 1996 entitled MULTIPLE ELECTRODE ABLATION APPARATUS, which is a continuation-in-part of U.S. Ser. No. 08/148,439 Nov. 8, 1993 now U.S. Pat. No. 5,458,597, issued Oct. 17, 1995, entitled DEVICE FOR TREATING CANCER AND NON-MALIGNANT TUMORS AND METHODS.

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates generally to an apparatus for the treatment and ablation of body masses, such as tumors, and more particularly, to a retractable multiple needle electrode apparatus that surrounds an exterior of a tumor with a plurality of needle electrodes and defines an ablative volume.

2. Description of Related Art

Current open procedures for treatment of tumors are extremely disruptive and cause a great deal of damage to healthy tissue. During the surgical procedure, the physician must exercise care in not cutting the tumor in a manor that creates seeding of the tumor, resulting in metastasis. In recent years development of products has been directed with an emphasis on minimizing the traumatic nature of traditional surgical procedures.

There has been a relatively significant amount of activity in the area of hyperthermia as a tool for treatment of tumors. It is known that elevating the temperature of tumors is helpful in the treatment and management of cancerous tissues. The mechanisms of selective cancer cell eradication by hyperthermia are not completely understood. However, four cellular effects of hyperthermia on cancerous tissue have been proposed, (i) changes in cell or nuclear membrane permeability or fluidity, (ii) cytoplasmic lysomal disintegration, causing release of digestive enzymes, (iii) protein thermal damage affecting cell respiration and the synthesis of DNA or RNA and (iv) potential excitation of immunologic systems. Treatment methods for applying heat to tumors include the use of direct contact radio-frequency (RF) applicators, microwave radiation, inductively coupled RF fields, ultrasound, and a variety of simple thermal conduction techniques.

Among the problems associated with all of these procedures is the requirement that highly localized heat be produced at depths of several centimeters beneath the surface of the body. Certain techniques have been developed with microwave radiation and ultrasound to focus energy at various desired depths. RF applications may be used at depth during surgery. However, the extent of localization is generally poor, with the result that healthy tissue may be harmed. Induction heating gives rise to poor localization of the incident energy as well. Although induction heating may be achieved by placing an antenna on the surface of the body, superficial eddy currents are generated in the immediate vicinity of the antenna. When it is driven using RF current unwanted surface heating occurs diminishing heating to the underlying tissue.

Thus, non-invasive procedures for providing heat to internal tumors have had difficulties in achieving substantial specific and selective treatment.

Hyperthermia, which can be produced from an RF or microwave source, applies heat to tissue but does not exceed 45 degrees C. so that normal cells survive. In thermotherapy, heat energy of greater than 45 degrees C. is applied, resulting in histological damage, desiccation and the denaturization of proteins. Hyperthermia has been applied more recently for therapy of malignant tumors. In hyperthermia, it is desirable to induce a state of hyperthermia that is localized by interstitial current heating to a specific area while concurrently insuring minimum thermal damage to healthy surrounding tissue. Often, the tumor is located subcutaneously and addressing the tumor requires either surgery, endoscopic procedures or external radiation. It is difficult to externally induce hyperthermia in deep body tissue because current density is diluted due to its absorption by healthy tissue. Additionally, a portion of the RF energy is reflected at the muscle/fat and bone interfaces which adds to the problem of depositing a known quantity of energy directly on a small tumor.

Attempts to use interstitial local hyperthermia have not proven to be very successful. Results have often produced nonuniform temperatures throughout the tumor. It is believed that tumor mass reduction by hyperthermia is related the thermal dose. Thermal dose is the minimum effective temperature applied throughout the tumor mass for a defined period of time. Because blood flow is the major mechanism of heat loss for tumors being heated, and blood flow varies throughout the tumor, more even heating of tumor tissue is needed to ensure more effective treatment.

The same is true for ablation of the tumor itself through the use of RF energy. Different methods have been utilized for the RF ablation of masses such as tumors. Instead of heating the tumor it is ablated through the application of energy. This process has been difficult to achieve due to a variety of factors including, (i) positioning of the RF ablation electrodes to effectively ablate all of the mass, (ii) introduction of the RF ablation electrodes to the tumor site and (iii) controlled delivery and monitoring of RF energy to achieve successful ablation without damage to non-tumor tissue.

There have been a number of different treatment methods and devices for minimally invasively treating tumors. One such example is an endoscope that produces RF hyperthermia in tumors, as disclosed in U.S. Pat. No. 4,920,978. A microwave endoscope device is described in U.S. Pat. No. 4,409,993. In U.S. Pat. No. 4,920,978, an endoscope for RF hyperthermia is disclosed.

In U.S. Pat. No. 4,763,671, a minimally invasive procedure utilizes two catheters that are inserted interstitially into the tumor. The catheters are placed within the tumor volume and each is connect to a high frequency power source.

In U.S. Pat. No. 4,565,200, an electrode system is described in which a single entrance tract cannula is used to introduce an electrode into a selected body site.

However, as an effective treatment device, electrodes must be properly positioned relative to the tumor. After the electrodes are positioned, it is then desirable to have controlled application and deposition of RF energy to ablate the tumor. This reduces destruction of healthy tissue.

There is a need for a RF tumor treatment apparatus that is useful for minimally invasive procedures. It would be desirable for such a device to surround the exterior of the tumor with treatment electrodes, defining a controlled ablation

volume, and subsequently the electrodes deliver a controlled amount of RF energy. Additionally, there is a need for a device with infusion capabilities during a pre-ablation step, and after ablation the surrounding tissue can be preconditioned with electromagnetic ("EM") energy at hyperthermia temperatures less than 45 degrees. This would provide for the synergistic affects of chemotherapy and the instillation of a variety of fluids at the tumor site after local ablation and hyperthermia.

SUMMARY OF THE INVENTION

An object of the invention is to provide an RF tissue ablation apparatus which ablates a desired tissue site, such as a tumor, in a minimally invasive manner.

Another object of the invention is to provide an RF tissue ablation apparatus which includes a selectable plurality of retractable electrodes which are advanced from a delivery catheter to define an ablation volume.

A further object of the invention is to provide an RF tissue ablation apparatus which includes a plurality of electrodes that are retractable to and from a delivery catheter. The electrodes are at least partially positioned in the delivery catheter in a non-deployed state, and become distended in a deployed state when advanced out a distal end of the delivery catheter, defining the ablation volume.

Another object of the invention is to provide an RF tissue ablation apparatus with deployed electrodes having a first section with a first radius of curvature, and a second section, that extends beyond the first section, having a second radius of curvature or a substantially linear geometry.

Yet another object of the invention is to provide an RF tissue ablation apparatus with deployed electrodes with two or more radii of curvature.

Still another object of the invention is to provide an RF tissue ablation apparatus with deployed electrodes having at least one radii of curvature in two or more planes.

A further object of the invention is to provide an RF tissue ablation apparatus with at least one deployed electrode that has one curved section located near a distal end of the delivery catheter, and a non-curved section extending beyond the curved section of the deployed electrode. The ablation apparatus also includes at least one deployed electrode with at least two radii of curvature.

Yet another object of the invention is to provide a tissue ablation apparatus with a plurality of retractable electrodes, each deployed electrode has at least one curved section located near a distal end of a delivery catheter, and a non-curved section which extends beyond the curved section of the deployed electrode.

These and other objects are attained with a tissue ablation apparatus that includes a delivery catheter, with distal and proximal ends. A handle is attached to the proximal end of the delivery catheter. An electrode deployment apparatus is positioned at least partially in the delivery catheter. It includes a plurality of electrodes that are retractable in and out of the catheter's distal end. The electrodes are in a non-deployed state when they are positioned within the delivery catheter. As they are advanced out the distal end of the catheter they become deployed, and define an ablation volume. Each electrode has a first section with a first radius of curvature, and a second section, extending beyond the first section, having a second radius of curvature or a substantially linear geometry.

Alternatively, each deployed electrode has at least two radii of curvature that are formed when the needle is advanced through the delivery catheter's distal end and becomes positioned at a selected tissue site.

In another embodiment, each deployed electrode has at least one radius of curvature in two or more planes. Further, the electrode deployment apparatus can include at least one deployed electrode having at least radii of curvature, and at least one deployed electrode with at least one radius of curvature in two or more planes.

In a further embodiment, the electrode deployment apparatus has at least one deployed electrode with at least one curved section that is located near the distal end of the delivery catheter, and a non-curved section which extends beyond the curved section of the deployed electrode. The electrode deployment apparatus also has at least one deployed electrode with at least two radii of curvature.

In another embodiment of the invention, each deployed electrode has at least one curved section located near the distal end of the delivery catheter, and a non-curved section that extends beyond the curved section of the deployed electrode.

An electrode template can be positioned at the distal end of the delivery catheter. It assists in guiding the deployment of the electrodes to a surrounding relationship at an exterior of a selected mass in a tissue. The electrodes can be hollow. An adjustable electrode insulator can be positioned in an adjacent, surrounding relationship to all or some of the electrodes. The electrode insulator is adjustable, and capable of being advanced and retracted along the electrodes in order to define an electrode conductive surface.

The electrode deployment apparatus can include a cam which advances and retracts the electrodes in and out of the delivery catheter's distal end. Optionally included in the delivery catheter are one or more guide tubes associated with one or more electrodes. The guide tubes are positioned at the delivery catheter's distal end.

Sources of infusing mediums, including but not limited to electrolytic and chemotherapeutic solutions, can be associated with the hollow electrodes. Electrodes can have sharpened, tapered ends in order to assist their introduction through tissue, and advancement to the selected tissue site.

The electrode deployment apparatus is removable from the delivery catheter. An obturator is initially positioned within the delivery catheter. It can have a sharpened distal end. The delivery catheter can be advanced percutaneously to an internal body organ, or site, with the obturator positioned in the delivery catheter. Once positioned, the obturator is removed, and the electrode deployment apparatus is inserted into the delivery catheter. The electrodes are in non-deployed states, and preferably compacted or spring-loaded, while positioned within the delivery catheter. They are made of a material with sufficient strength so that as the electrodes emerge from the delivery catheter's distal end they are deployed three dimensionally, in a lateral direction away from the periphery of the delivery catheter's distal end. The electrodes continue their lateral movement until the force applied by the tissue causes the needles to change their direction of travel.

Each electrode now has either, (i) a first section with a first radius of curvature, and a second section, extending beyond the first section, having a second radius of curvature or a substantially linear section, (ii) two radii of curvature, (iii) one radius of curvature in two or more planes, or (iv) a combination of two radii of curvature with one of them in two or more planes. Additionally, the electrode deployment apparatus can include one or more of these deployed geometries for the different electrodes in the plurality. It is not necessary that every electrode have the same deployed geometry.

After the electrodes are positioned around a mass, such as a tumor, a variety of solutions, including but not limited to electrolytic fluids, can be introduced through the electrodes to the mass in a pre-ablation step. RF energy is applied, and the mass is desiccated. In a post-ablation procedure, a chemotherapeutic agent can then be introduced to the site, and the electrodes are then retracted back into the introducing catheter. The entire ablative apparatus can be removed, or additional ablative treatments be conducted.

BRIEF DESCRIPTION OF THE FIGURES

FIG. **1** is a perspective view of the tissue ablation apparatus of the invention, including a delivery catheter, handle, and deployed electrodes.

FIG. **2** is a cross-sectional view of the tissue ablation apparatus of the invention illustrated in FIG. **1**.

FIG. **3** is a perspective view of an electrode of the invention with two radii of curvature.

FIG. **4** is a perspective view of an electrode of the invention with one radius of curvature in three planes.

FIG. **5** is a perspective view of an electrode of the invention with one curved section, positioned close to the distal end of the delivery catheter, and a linear section.

FIG. **6** is a perspective view of an electrode of the invention with one curved section, positioned close to the distal end of the delivery catheter, a generally first linear section, and then a second linear section that continues laterally with regard to the first linear section.

FIG. **7** is a cross-section view of a delivery catheter associated with the invention, with guide tubes positioned at the distal end of the delivery catheter.

FIG. **8** is a cross-sectional view of an electrode of the invention.

FIG. **9** is a perspective view of the tissue ablation apparatus of the invention shown in FIG. **1**, with the delivery catheter being introduced percutaneously through the body and positioned at the exterior, or slightly piercing, a liver with a tumor to be ablated.

FIG. **10** is a perspective view of the tissue ablation apparatus of the invention with an obturator positioned in the delivery catheter.

FIG. **11** is a perspective view of the tissue ablation apparatus of the invention shown in FIG. **10**, positioned in the body adjacent to the liver, with the obturator removed.

FIG. **12** is a perspective view of the tissue ablation apparatus of the invention shown in FIG. **10**, positioned in the body adjacent to the liver, and the electrode deployment apparatus, with an electrode template, is positioned in the delivery catheter in place of the obturator.

FIG. **13** is a perspective view of the ablation apparatus of the invention, with deployed electrodes surrounding a tumor and defining an ablation volume.

FIG. **14** is a perspective view of the tissue ablation apparatus of the invention shown in FIG. **10**, positioned in the body adjacent to the liver, with deployed electrodes surrounding a tumor and infusing a solution to the tumor site during a pre-ablation procedure.

FIG. **15** is a perspective view of the tissue ablation apparatus of the invention shown in FIG. **10**, illustrating application of RF energy to the tumor.

FIG. **16** is a perspective view of the tissue ablation apparatus of the invention, illustrating the electrodesiccation of the tumor.

FIG. **17** is a perspective view of the tissue ablation apparatus of the invention, illustrating the instillation of solutions to the tumor site during a postablation procedure.

FIG. **18** illustrates bipolar ablation between electrodes of the invention.

FIG. **19** illustrates monopolar ablation between electrodes of the invention.

FIG. **20** is a perspective view of an ablation system of the invention, including RF and ultrasound modules, and a monitor.

FIG. **21** is a block diagram of the ablation system of the invention.

DETAILED DESCRIPTION

A tissue ablation apparatus **10** of the invention is illustrated in FIG. **1**. Ablation apparatus **10** includes a delivery catheter **12**, well known to those skilled in the art, with a proximal end **14** and a distal end **16**. Delivery catheter **12** can be of the size of about 5 to 16 F. A handle **18** is removably attached to proximal end **14**. An electrode deployment device is at least partially positioned within delivery catheter **12**, and includes a plurality of electrodes **20** that are retractable in and out of distal end **16**. Electrodes **20** can be of different sizes, shapes and configurations. In one embodiment, they are needle electrodes, with sizes in the range of 27 to 14 gauge. Electrodes **20** are in non-deployed positions while retained in delivery catheter. In the non-deployed positions, electrodes **20** may be in a compacted state, spring loaded, generally confined or substantially straight if made of a suitable memory metal such as nitinol. As electrodes **20** are advanced out of distal end **16** they become distended in a deployed state, which defines an ablative volume, from which tissue is ablated as illustrated more fully in FIG. **2**. Electrodes **20** operate either in the bipolar or monopolar modes. When the electrodes are used in the bipolar mode, the ablative volume is substantially defined by the peripheries of the plurality of electrodes **20**. In one embodiment, the cross-sectional width of the ablative volume is about 4 cm. However, it will be appreciated that different ablative volumes can be achieved with tissue ablation apparatus **10**.

The ablative volume is first determined to define a mass, such as a tumor, to be ablated.

Electrodes **20** are placed in a surrounding relationship to a mass or tumor in a predetermined pattern for volumetric ablation. An imaging system is used to first define the volume of the tumor or selected mass. Suitable imaging systems include but are not limited to, ultrasound, computerized tomography (CT) scanning, X-ray film, X-ray fluoroscopy, magnetic resonance imaging, electromagnetic imaging, and the like. The use of such devices to define a volume of a tissue mass or a tumor is well known to those skilled in the art.

With regard to the use of ultrasound, an ultrasound transducer transmits ultrasound energy into a region of interest in a patient's body. The ultrasound energy is reflected by different organs and different tissue types. Reflected energy is sensed by the transducer, and the resulting electrical signal is processed to provide an image of the region of interest. In this way, the ablation volume is then ascertained, and the appropriate electrode deployment device is inserted into delivery catheter **12**.

The ablative volume is substantially defined before ablation apparatus **10** is introduced to an ablative treatment position. This assists in the appropriate positioning of ablation apparatus **10**. In this manner, the volume of ablated tissue is reduced and substantially limited to a defined mass or tumor, including a certain area surrounding such a tumor, that is well controlled and defined. A small area around the tumor is ablated in order to ensure that all of the tumor is ablated.

With reference again to FIG. **2**, electrode sections **20**(*a*) are in deployed states when they are introduced out of distal end **16**. Although electrodes **20** are generally in a non-distended configuration in the non-deployed state while positioned in delivery catheter **12**, they can also be distended. Generally, electrode sections **20**(*b*) are in retained positions while they are non-deployed. This is achieved by a variety of methods including but not limited to, (i) the electrodes are pre-sprung, confined in delivery catheter **12**, and only become sprung (expanded) as they are released from delivery catheter **12**, (ii) the electrodes are made of a memory metal, as explained in further detail below, (iii) the electrodes are made of a selectable electrode material which gives them an expanded shape outside of delivery catheter **12**, or (iv) delivery catheter **12** includes guide tubes which serve to confine electrodes **12** within delivery catheter **12** and guide their direction of travel outside of the catheter to form the desired, expanded ablation volume. As shown in FIG. **2**, electrodes **20** are pre-sprung while retained in delivery catheter **12**. This is the non-deployed position. As they are advanced out of delivery catheter **12** and into tissue, electrodes **20** become deployed and begin to "fan" out from distal end **16**, moving in a lateral direction relative to a longitudinal axis of delivery catheter **12**. As deployed electrodes **20** continue their advancement, the area of the fan increases and extends beyond the diameter of distal end **16**.

Significantly, each electrode **20** is distended in a deployed position, and collectively, the deployed electrodes **20** define a volume of tissue that will be ablated. As previously mentioned, when it is desired to ablate a tumor, either benign or malignant, it is preferable to ablate an area that is slightly in excess to that defined by the exterior surface of the tumor. This improves the chances that all of the tumor is eradicated.

Deployed electrodes **20** can have a variety of different deployed geometries including but not limited to, (i) a first section with a first radius of curvature, and a second section, extending beyond the first section, having a second radius of curvature or a substantially linear geometry, (ii) at least two radii of curvature, (iii) at least one radius of curvature in two or more planes, (iv) a curved section, with an elbow, that is located near distal end **16** of delivery catheter, and a non-curved section that extends beyond the curved section, or (v) a curved section near distal end **16**, a first linear section, and then another curved section or a second linear section that is angled with regard to the first linear section. Deployed electrodes **20** need not be parallel with respect to each other. The plurality of deployed electrodes **20**, which define a portion of the needle electrode deployment device, can all have the same deployed geometries, i.e., all with at least two radii of curvature, or a variety of geometries, i.e., one with two radii of curvature, a second one with one radius of curvature in two planes, and the rest a curved section near distal end **16** of delivery catheter **12** and a non-curved section beyond the curved section.

A cam **22**, or other actuating device, can be positioned within delivery catheter and used to advance and retract electrodes **20** in and out of delivery catheter **12**. The actual movement of cam can be controlled at handle **18**. Suitable cams are of conventional design, well known to those skilled in the art.

The different geometric configurations of electrodes **20** are illustrated in FIGS. **3** through **6**. In FIG. **3**, electrode **20** has a first radius of curvature **20**(*c*) and a second radius of curvature **20**(*d*). It can include more than two radii of curvature. As shown in FIG. **4**, electrode **20** has at least one radius of curvature which extends to three planes. In FIG. **5**, each electrode has a first curved section **20**(*e*) which is near distal end **16** of delivery catheter **12**. A first generally linear section **20**(*f*) extends beyond curved section **20**(*e*), and the two meet at an elbow **20**(*g*). The electrodes **20** can serve as anodes and cathodes. The plurality of electrodes **20** can have linear sections **20**(*f*) that are generally parallel to each other, or they can be non-parallel. FIG. **6** illustrates an electrode **20** that includes a first curved section **20**(*e*) positioned near distal end **16** of delivery catheter **12**, a first linear section **20**(*f*), and a second linear section **20**(*h*) which extends beyond first linear section **20**(*f*). Section **20**(*h*) can be linear, curved, or a combination of the two. The plurality of electrodes **20** illustrated in FIG. **6** can have parallel or non-parallel first linear sections **20**(*f*).

In one embodiment of the invention, electrodes **20** are spring-loaded, and compacted in their non-deployed positions. As electrodes **20** are advanced out of distal end **16** of delivery catheter **12**, they become deployed and fan out. Electrodes **20** continue this fanning out direction until the resistance of the tissue overcomes the strength of the material forming electrode **20**. This causes electrode **20** to bend and move in a direction inward relative to its initial outward fanning direction. The bending creates curved sections **20**(*c*) and **20**(*d*) of FIG. **3**, and can also result in the formation of the other electrode **20** geometries of FIGS. **4**, **5** and **6**. The extent of electrode **20** fan like travel is dependent on the strength of the material from which it is made. Suitable electrode materials include stainless steel, platinum, gold, silver, copper and other electromagnetic conducting materials including conductive polymers. Preferably, electrode **20** is made of stainless steel or nickel titanium and has dimensions of about 27 to 14 gauge.

In one embodiment, electrode **20** is made of a memory metal, such as nickel titanium, commercially available from Raychem Corporation, Menlo Park, Calif. Additionally, a resistive heating element can be positioned in an interior lumen of electrode **20**. Resistive heating element can be made of a suitable metal that transfers heat to electrode **20**, causing deployed electrode **20** to become deflected when the temperature of electrode **20** reaches a level that causes the electrode material, such as a memory metal, to deflect, as is well known in the art. Not all of electrode **20** need be made of a memory metal. It is possible that only that distal end portion of electrode **20**, which is introduced into tissue, be made of the memory metal in order to effect the desired deployed geometrical configuration. Additionally, mechanical devices, including but not limited to steering wires, can be attached to the distal end of electrode **20** to cause it to become directed, deflected and move about in a desired direction about the tissue, until it reaches its final resting position to ablate a tissue mass.

Optionally included in the delivery catheter are one or more guide tubes **24**, FIG. **7**, which serve to direct the expansion of electrodes **20** in the fan pattern as they are advanced out of distal end **16** of the delivery catheter **12**. Guide tubes **24** can be made of stainless steel, spring steel and thermal plastics including but not limited to nylon and polyesters, and are of sufficient size and length to accommodate the electrodes to a specific site in the body.

FIG. **8** illustrates one embodiment of electrode **20** with a sharpened distal end **24**. By including a tapered, or piercing end **24**, the advancement of electrode **20** through tissue is easier. Electrode **20** can be segmented, and include a plurality of fluid distribution ports **26**, which can be evenly formed around all or only a portion of electrode **20**. Fluid distribution ports **26** are formed in electrode **20** when it is hollow and permit the introduction and flow of a variety of fluidic mediums through electrode **20** to a desired tissue site.

Such fluidic mediums include, but are not limited to, electrolytic solutions, pastes or gels, as well as chemotherapeutic agents. Examples of suitable conductive gels are carboxymethyl cellulose gels made from aqueous electrolyte solutions such as physiological saline solutions, and the like.

The size of fluid distribution ports **26** can vary, depending on the size and shape of electrode **20**. Also associated with electrode **20** is an adjustable insulator sleeve **28** that is sidable along an exterior surface of electrode **20**. Insulator sleeve **28** is advanced and retracted along electrode **20** in order to define the size of a conductive surface of electrode **20**. Insulator sleeve **28** is actuated at handle **18** by the physician, and its position along electrode **20** is controlled. When electrode **20** moves out of delivery catheter **12** and into tissue, insulator sleeve **28** can be positioned around electrode **20** as it moves its way through the tissue.

Alternatively, insulator sleeve **28** can be advanced along a desired length of electrode **20** after electrode **20** has been positioned around a targeted mass to be ablated. Insulator sleeve is thus capable of advancing through tissue along with electrode **20**, or it can move through tissue without electrode **20** providing the source of movement. Thus, the desired ablation volume is defined by deployed electrodes **20**, as well as the positioning of insulator sleeve **28** on each electrode. In this manner, a very precise ablation volume is created. Suitable materials that form insulator sleeve include but are not limited to nylon, polyimides, other thermoplastics, and the like.

FIG. **9** illustrates a percutaneous application of tissue ablation apparatus **10**. Tissue ablation apparatus **10** can be used percutaneously to introduce electrodes **20** to the selected tissue mass or tumor. Electrodes **20** can remain in their non-deployed positions while being introduced percutaneously into the body, and delivered to a selected organ which contains the selected mass to be ablated. Delivery catheter **12** is removable from handle **18**. When it is removed, electrode deployment device (the plurality of electrodes **20**) can be inserted and removed from delivery catheter **12**. An obturator **30** is inserted into delivery catheter **12** initially if a percutaneous procedure is to be performed. As shown in FIG. **10**, obturator **30** can have a sharpened distal end **32** that pierces tissue and assists the introduction of delivery catheter **12** to a selected tissue site. The selected tissue site can be a body organ with a tumor or other mass, or the actual tumor itself.

Obturator **30** is then removed from delivery catheter **12** (FIG. **11**). Electrode deployment device is then inserted into delivery catheter **12**, and the catheter is then reattached to handle **18** (FIG. **12**). As illustrated in FIG. **12**, electrode deployment device can optionally include an electrode template **34** to guide the deployment of electrodes **20** to a surrounding relationship at an exterior of a selected mass in the tissue.

Electrodes **20** are then advanced out of distal end **16** of delivery catheter **12**, and become deployed to form a desired ablative volume which surrounds the mass. In FIG. **13**, delivery catheter **12** is positioned adjacent to the liver. Electrode deployment device is introduced into delivery catheter **12** with electrode template **34**. Electrode deployment device now pierces the liver, and cam **22** advances electrodes **20** out of delivery catheter **12** into deployed positions. Each individual electrode **20** pierces the liver and travels through it until it is positioned in a surrounding relationship to the tumor. The ablative volume is selectable, and determined first by imaging the area to be ablated. The ablative volume is defined by the peripheries of all of the deployed electrodes **20** that surround the exterior of the tumor. Once the volume of ablation is determined, then an electrode set is selected which will become deployed to define the ablation volume. A variety of different factors are important in creating an ablation volume. Primarily, different electrodes **20** will have various degrees of deployment, based on type of electrode material, the level of prespringing of the electrodes and the geometric configuration of the electrodes in their deployed states. Tissue ablation apparatus **10** permits different electrode **20** sets to be inserted into delivery catheter **12**, in order to define a variety of ablation volumes.

Prior to ablation of the tumor, a pre-ablation step can be performed. A variety of different solutions, including electrolytic solutions such as saline, can be introduced to the tumor site, as shown in FIG. **14**. FIG. **15** illustrates the application of RF energy to the tumor. Electrode insulator **28** is positioned on portions of electrodes **20** where there will be no ablation. This further defines the ablation volume. The actual electro-desiccation of the tumor, or other targeted masses or tissues, is shown in FIG. **16**. Again, deployed electrodes **20**, with their electrode insulators **28** positioned along sections of the electrodes, define the ablation volume, and the resulting amount of mass that is desiccated.

Optionally following desiccation, electrodes **20** can introduce a variety of solutions in a post-ablation process. This step is illustrated in FIG. **17**. Suitable solutions include but are not limited to chemotherapeutic agents.

FIG. **8** illustrates tissue ablation apparatus **10** operated in a bipolar mode. Its monopolar operation is shown in FIG. **19**. Each of the plurality of electrodes **20** can play different roles in the ablation process. There can be polarity shifting between the different electrodes.

A tissue ablation system **36**, which can be modular, is shown in FIG. **20** and can include a display **38**. Tissue ablation system **36** can also include an REF energy source, microwave source, ultrasound source, visualization devices such as cameras and VCR's, electrolytic and chemotherapeutic solution sources, and a controller which can be used to monitor temperature or impedance. One of the deployed electrodes **20** can be a microwave antenna coupled to a microwave source. This electrode can initially be coupled to RF power source **42** and is then switched to the microwave source

Referring now to FIG. **21**, a power supply **40** delivers energy into RF power generator (source) **42** and then to electrodes **20** of tissue ablation apparatus **10**. A multiplexer **46** measures current, voltage and temperature (at numerous temperature sensors which can be positioned on electrodes **20**). Multiplexer **46** is driven by a controller **48**, which can be a digital or analog controller, or a computer with software. When controller **48** is a computer, it can include a CPU coupled through a system bus. This system can include a keyboard, disk drive, or other non-volatile memory systems, a display, and other peripherals, as known in the art. Also coupled to the bus are a program memory and a data memory.

An operator interface **50** includes operator controls **52** and display **38**. Controller **48** is coupled to imaging systems, including ultrasound transducers, temperature sensors, and viewing optics and optical fibers, if included.

Current and voltage are used to calculate impedance. Diagnostics are done through ultrasound, CT scanning, or other methods known in the art. Imaging can be performed before, during and after treatment.

Temperature sensors measure voltage and current that is delivered. The output of these sensors is used by controller

48 to control the delivery of RF power. Controller 48 can also control temperature and power. The amount of RF energy delivered controls the amount of power. A profile of power delivered can be incorporated in controller 38, as well as a pre-set amount of energy to be delivered can also be profiled.

Feedback can be the measurement of impedance or temperature, and occurs either at controller 48 or at electromagnetic energy source 42, e.g., RF or microwave, if it incorporates a controller. For impedance measurement, this can be achieved by supplying a small amount of non-ablation RF energy. Voltage and current are then measured.

Circuitry, software and feedback to controller 48 result in process control and are used to change, (i) power, including RF, ultrasound, and the like, (ii) the duty cycle (on-off and wattage), (iii) monopolar or bipolar energy delivery, (iv) chemotherapeutic and electrolytic solution delivery, flow rate and pressure and (v) determine when ablation is completed through time, temperature and/or impedance. These process variables can be controlled and varied based on temperature monitored at multiple sites, and impedance to current flow that is monitored, indicating changes in current carrying capability of the tissue during the ablative process.

The foregoing description of preferred embodiments of the present invention has been provided for the purposes of illustration and description. It is not intended to be exhaustive or to limit the invention to the precise forms disclosed. Obviously, many modifications and variations will be apparent to practitioners skilled in this art. The embodiments were chosen and described in order to best explain the principles of the invention and its practical application, thereby enabling others skilled in the art to understand the invention for various embodiments and with various modifications as are suited to the particular use contemplated. It is intended that the scope of the invention be defined by the following claims and their equivalents.

What is claimed is:

1. A tissue ablation apparatus, comprising:

an introducer having a distal portion and a proximal portion;

an electrode device positionable within an interior of the introducer as the introducer is advanced through tissue, the electrode device including at least a first RF electrode, a second RF electrode and a third RF electrode, each of the first, second and third RF electrodes having a tissue piercing distal end, a non-deployed state when positioned within the introducer and a deployed state when advanced from the distal portion of the introducer, the first, second and third RF electrodes being deployable with curvature from the introducer distal portion and including a section that is perpendicular to a longitudinal axis of the introducer, the first, second and third RF electrodes exhibiting a changing direction of travel along a length of each electrode deployed from the introducer;

an electrode advancement and retraction member coupled to the electrode device to advance the first, second and third RF electrodes in and out of the introducer distal portion.

2. The apparatus of claim 1, wherein the RF electrodes are retractable in and out of the distal portion of the introducer.

3. The apparatus of claim 1, wherein the ablation volume is defined substantially by the peripheries of the RF electrodes in the deployed state.

4. The apparatus of claim 1, wherein the ablation volume is defined between the RF electrodes in their deployed states.

5. The apparatus of claim 1, wherein the RF electrodes in their deployed state define a three-dimensional ablation volume.

6. The apparatus of claim 1, wherein the RF electrodes are pre-sprung while retained in the introducer such that on being advanced from the distal portion of the introducer the RF electrodes become deployed and fan out from the distal portion of the introducer.

7. The apparatus of claim 1, wherein the RF electrodes are pre-sprung while retained in the introducer such that on being advanced from the distal portion of the introducer the RF electrodes become deployed and fan out from the distal portion of the introducer through tissue in accordance with the curvature.

8. The apparatus of claim 1, wherein each of the RF electrodes changes direction along a length of the electrode in the deployed state.

9. The apparatus of claim 1, wherein at least one of the RF electrodes exhibits, in the deployed state, at least one curved section located near the distal portion of the introducer and a non-curved section beyond the curved section.

10. The apparatus of claim 1, wherein at least one of the RF electrodes exhibits, in the deployed state, a first section which has a first radius of curvature and a second section which extends beyond the first section and has a second radius of curvature.

11. The apparatus of claim 1, wherein at least one of the RF electrodes exhibits, in the deployed state, at least two radii of curvature.

12. The apparatus of claim 1, wherein at least one of the RF electrodes exhibits, in the deployed state, at least two radii of curvature in one plane.

13. The apparatus of claim 1, wherein at least one of the RF electrodes exhibits, in the deployed state, at least two radii of curvature in at least two planes.

14. The apparatus of claim 1, wherein each RF electrode is made of a memory metal or a sprung steel.

15. The apparatus of claim 1. wherein each RF electrode is hollow and includes a fluid distribution port.

16. The apparatus of claim 15, further comprising a source of infusing medium coupled to each of the RF electrodes.

17. The apparatus of claim 15, further comprising a source of chemotherapeutic agent coupled to each of the RF electrodes.

18. The apparatus of claim 1, further comprising an electrode insulator positioned adjacent to and in surrounding relationship to each of the RF electrodes to define an electrode energy delivery surface.

19. The apparatus of claim 1, wherein the electrode advancement and retraction member is removable from the introducer.

20. The apparatus of claim 1, further comprising:

a handle member coupled to the introducer.

21. The apparatus of claim 1, wherein each RF electrode is wire-like.

22. The apparatus of claim 1, wherein each RF electrode includes a hollow lumen.

23. The apparatus of claim 1, further comprising:

an energy source coupled to the RF electrodes.

24. The apparatus of claim 23, wherein the energy source is an RF source coupled to the RF electrodes.

25. The apparatus of claim 23 further comprising:

a thermal sensor coupled to electrode device.

26. The apparatus of claim 1, wherein the first second and third RF electrodes are bipolar RF electrodes.

27. The apparatus of claim 1, wherein the first second and third RF electrodes are monopolar electrodes.

28. A method of deploying electrodes for defining an ablation volume, the method comprising:

providing an ablation apparatus including at least a first RF electrode, a second RF electrode and an introducer with a proximal portion and a distal portion, each of the RF electrodes having a tissue piercing distal end and configured to be advanceable from the introducer distal with curvature from a non-deployed state when positioned within the introducer to a deployed state when advanced from the introducer distal portion, each of the RF electrodes including a section that is perpendicular to a longitudinal axis of the introducer in the deployed state, the first and second RF electrodes exhibiting a changing direction of travel along a length of electrode deployed from the introducer;

positioning the introducer in a solid tissue mass to a selected tissue site; and

advancing the first and second RF electrodes from the distal portion of the introducer to the deployed state.

29. The method of claim 28 further comprising:

retracting the RF electrodes in and out of the distal portion of the introducer.

30. The method of claim 28 further comprising:

inserting the RF electrodes into tissue so as to penetrate the tissue.

31. The method of claim 28, wherein the ablation volume is substantially defined by the peripheries of the RF electrodes in the deployed state.

32. The method of claim 28, wherein the ablation volume is defined between the deployed RF electrodes.

33. A method of claim 28 further comprising:

deploying the RF electrodes to define a three-dimensional ablation volume.

34. The method of claim 28 further comprising:

advancing the RF electrodes from the distal portion of the introducer such that the RF electrodes become deployed and fan out from the distal portion.

35. The method of claim 28, wherein the RF electrodes are pre-sprung while retained in the introducer such that on being advanced from the distal portion of the introducer the RF electrodes become deployed and fan out from the distal portion of the introducer through tissue in accordance with the radius of curvature.

36. A method of claim 28, wherein at least one of the RF electrodes changes direction along its length in the deployed state.

37. A tissue ablation apparatus, comprising:

an introducer having a distal portion, a distal end at a distal most position of the distal portion, an introducer aperture formed at the distal end and a proximal portion;

an electrode device positionable within an interior of the introducer as the introducer is advanced through tissue, the electrode device including at least a first RF electrode, a second RF electrode and a third RF electrode, each of the first, second and third RF electrodes having a tissue piercing distal end, a non-deployed state when positioned within the introducer and a deployed state when advanced from the distal end of the introducer, the first, second and third RF electrodes being deployable with cuvature from the introducer distal end and including a section that is perpendicular to a longitudinal axis of the introducer, the first, second and third RF electrodes exhibiting a changing direction of travel along a length of each electrode deployed from the introducer; and

an electrode advancement and retraction member coupled to the electrode device, the electrode advancement and retraction member advancing and retracting the RF electrodes in and out of the introducer distal end.

38. A tissue ablation apparatus, comprising:

an introducer having a distal portion, a distal end and a proximal portion;

an electrode device positionable within an interior of the introducer as the introducer is advanced through tissue, the electrode device including at least a first RF electrode, a second RF electrode and a third RF electrode, each of the first, second and third RF electrodes having a non-deployed state when positioned within the introducer and a deployed state when advanced from the distal end of the introducer, the first, second and third RF electrodes being deployable with curvature from the introducer distal end to define an ablation volume, the first, second and third RF electrodes exhibiting a changing direction of travel along a length of each electrode deployed from the introducer; and

an electrode advancement and retraction member coupled to the electrode device, the electrode advancement and retraction member advancing and retracting the RF electrodes in and out of the introducer distal end.

39. The apparatus of claim 38, further including an impedance measurement apparatus coupled to the electrode device.

40. A tissue ablation apparatus, comprising:

a rigid introducer having a distal portion and a proximal portion;

an electrode device positionable within an interior of the introducer as the introducer is advanced through tissue, the electrode device including at least a first RF electrode with a tissue piercing distal end and a second RF electrode with a tissue piercing distal end, each of the first and second RF electrodes having a non-deployed state when positioned within the introducer and a deployed state when advanced from the distal portion of the introducer, the first and second RF electrodes being deployable with curvature from the introducer distal portion, the first and second RF electrodes exhibiting a changing direction of travel along a length of each electrode deployed from the introducer; and

an electrode advancement and retraction member coupled to the electrode device, the electrode advancement and retraction member advancing and retracting the RF electrodes in and out of the introducer distal portion.

41. A tissue ablation apparatus, comprising:

an introducer having a distal portion and a proximal portion;

an electrode device positionable within an interior of the introducer as the introducer is advanced through tissue, the electrode device including at least a first RF electrode with a tissue piercing distal end, a second RF electrode with a tissue piercing distal end and an electrode coupling, each of the first and second RF electrodes having a non-deployed state when positioned within the introducer and a deployed state when advanced from the distal portion of the introducer, the first and second RF electrodes being deployable with curvature from the introducer distal portion, the first and second RF electrodes exhibiting a changing direction of travel along a length of each electrode deployed from the introducer; and

an electrode advancement and retraction member coupled to the electrode device, the electrode advancement and

retraction member advancing and retracting the RF electrodes in and out of the introducer distal end, wherein the electrode device is physically coupled to the electrode advancement and retraction member.

42. The apparatus of claim **41**, wherein the electrode advancement member is a rigid electrode introducer.

43. The apparatus of claim **42**, further comprising:

a handpiece coupled of the rigid electrode introducer.

44. The apparatus of claim **43**, wherein the rigid electrode introducer is coupled to the handpiece.

45. A tissue ablation apparatus, comprising:

an introducer having a distal portion and a proximal portion;

an obturator with a tissue piercing distal end, the obturator being positionable in an interior of the introducer as the obturator is advanced through tissue;

an electrode device positionable within the interior of the introducer, the electrode device including at least a first RF electrode, a second RF electrode and a third RF electrode, each of the first, second and third RF electrodes having a tissue piercing distal end, a non-deployed state when positioned within the introducer and a deployed state when advanced from the distal portion of the introducer, the first, second and third RF electrodes being deployable with curvature from the introducer distal portion and including a section that is perpendicular to a longitudinal axis of the introducer, the first, second and third RF electrodes exhibiting a changing direction of travel along a length of each electrode deployed from the introducer; and

an electrode advancement and retraction member coupled to the electrode device to advance the first, second and third RF electrodes in and out of the introducer distal portion.

46. A tissue ablation apparatus, comprising:

an introducer having a distal portion and a proximal portion;

an obturator with a tissue piercing distal end, the obturator being positionable in an interior of the introducer as the obturator is advanced through tissue;

an electrode device positionable within the interior of the introducer, the electrode device including an electrode housing and at least a first RF electrode, a second RF electrode and a third RF electrode positionable in the electrode housing, each of the first, second and third RF electrodes having a tissue piercing distal end, a non-deployed state when positioned within the electrode housing and a deployed state when advanced from the distal portion of the introducer, the first, second and third RF electrodes being deployable with curvature from the introducer distal portion and including a section that is perpendicular to a longitudinal axis of the introducer, the first, second and third RF electrodes exhibiting a changing direction of travel along a length of each electrode deployed from the introducer; and

an electrode advancement and retraction member coupled to the electrode device to advance the first, second and third RF electrodes in and out of the introducer distal portion.

* * * * *

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VanTassel et al.

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(45) **Date of Patent: Jun. 5, 2001**

(54) **HYPODERMIC NEEDLE WITH WEEPING TIP AND METHOD OF USE**

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(52) **U.S. Cl.** **604/272**; 604/264

(58) **Field of Search** 604/272, 264, 604/273, 274, 275

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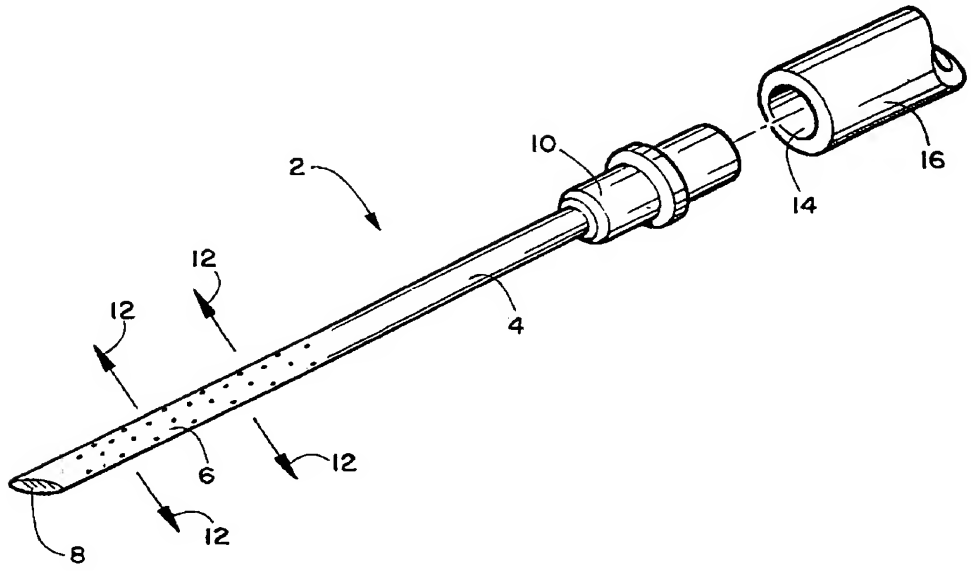
(74) *Attorney, Agent, or Firm*—Oppenheimer Wolff & Donnelly, LLP

(57) **ABSTRACT**

The invention provides surgical needles with a porous distal portion from which a liquid injectate will weep or ooze multidirectionally under injection pressure while the porous distal portion of the needle is inserted into a body surface. The porous distal portion of the needle can be fabricated from a porous carbon, metal, ceramic or polymer and preferably has a decreasing gradient of impedance to fluid flowing to the point of the needle to compensate for the falling off of injection pressure as fluid moves towards the point, thereby ensuring uniform weeping of the injectate along the injection course. The needle is adapted for attachment to a catheter or syringe. In another embodiment, a surgical assemblage is provided wherein a porous distal portion having similar fluid flow characteristics is located along the distal end of a catheter, and a needle point is attached to the distal end of the catheter (e.g., a steerable catheter) for piercing tissue. A guidance catheter can be used to direct the invention devices to a remote internal injection site. The invention devices and methods can be used to inject fluids (including those containing nucleic acids for gene therapy) into interior body walls or tissue, such as a beating heart, without substantial loss of fluid and without substantial damage to tissue caused by injectate.

44 Claims, 1 Drawing Sheet



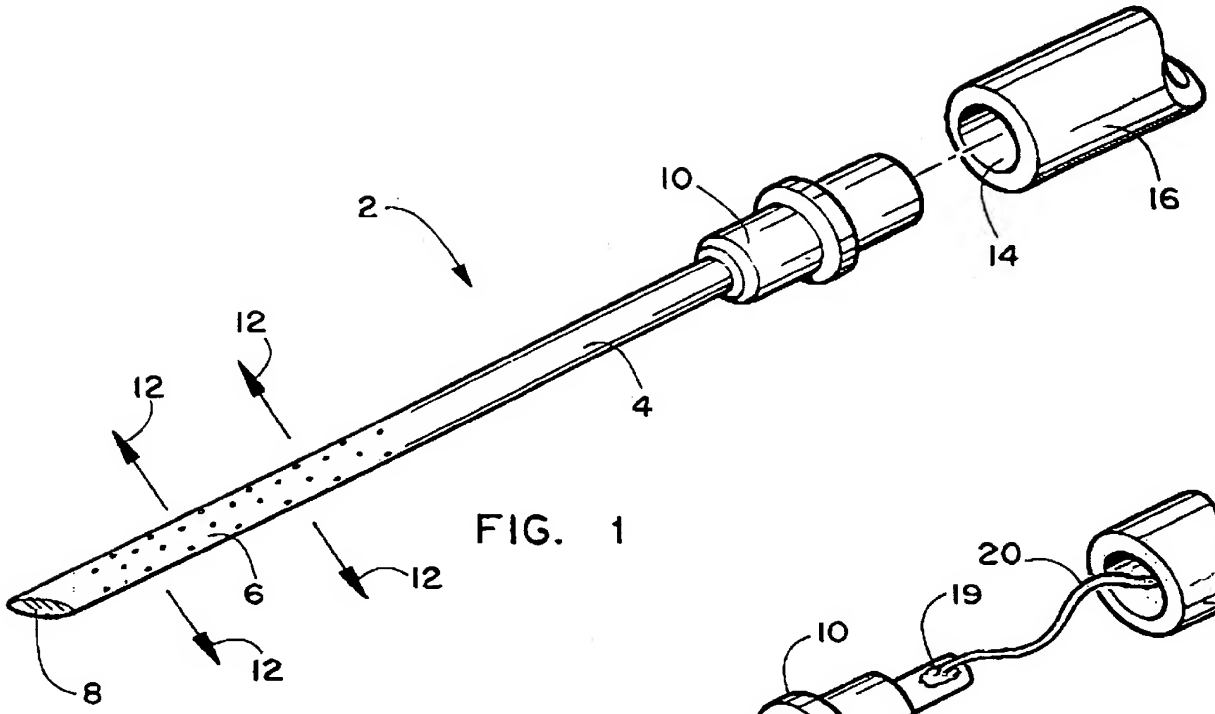


FIG. 1

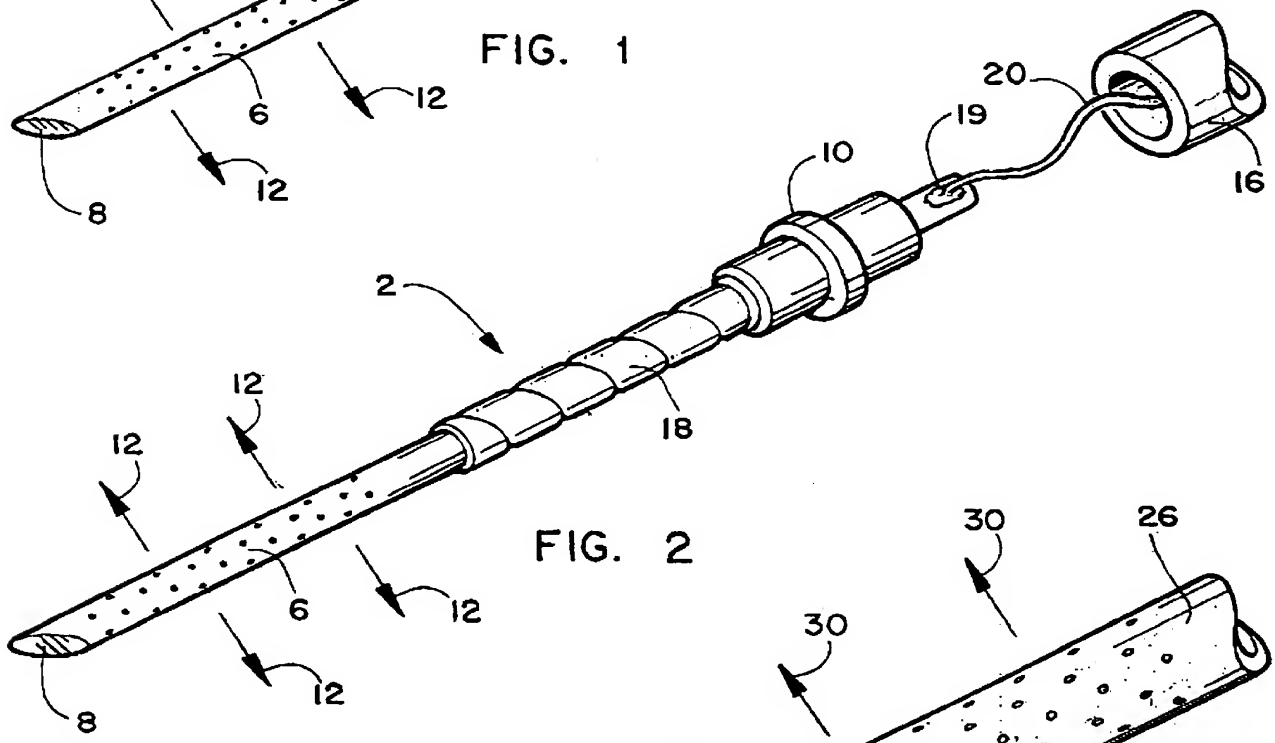


FIG. 2

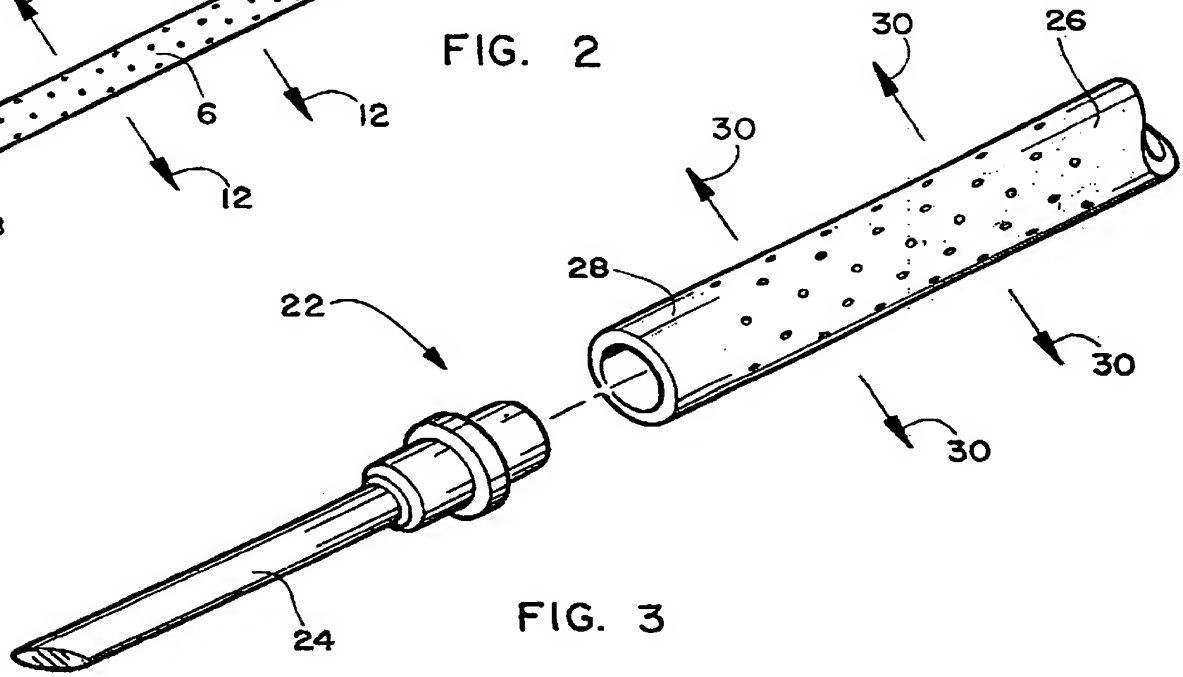


FIG. 3

HYPODERMIC NEEDLE WITH WEEPING TIP AND METHOD OF USE

FIELD OF THE INVENTION

The present invention generally relates to surgical instruments and to instruments used to inject medicaments into a body wall or tissue.

BACKGROUND OF THE INVENTION

The direct introduction of a drug, compound, biologically active peptide or protein into the cells of a patient can have significant therapeutic value. However, this approach also has several drawbacks. Of primary concern is the risk of potential toxicity, particularly at dosages sufficient to produce a biological response to the peptide. From a practical perspective, there is also the problem of the cost associated with isolating and purifying or synthesizing the peptides. Moreover, the clinical impact of the peptides is also limited by their relatively short half-life in vivo, which usually results from their degradation by any proteases present in the target tissue.

For these reasons, introduction of bioactive agents, including proteins, into a patient by delivery of a gene or a cell containing a gene that will express a therapeutic protein in the patient/host is an intriguing alternative to administering the substance. However, to date the principal means for introduction of foreign genetic material into a host has involved the integration of the gene into the host genome by, for example, transforming the host's cells with a viral vector. Direct in vivo gene transfer into postnatal animals has also been reported using DNA encapsulated in liposomes including DNA entrapped in proteoliposomes containing viral envelope receptor proteins.

With respect to delivery systems for genes, means such as viral vectors which introduce the gene into the host's genome can present potential health risks associated with damage to the genetic material in the host cell. Use of cationic liposomes or a biolistic device (i.e., a vaccine "gun" which "shoots" polynucleotides coupled to beads into tissue) to deliver genes in vivo is preparation intensive and, in some cases, requires some experimentation to select proper particle sizes for transmission into target cells. Further, any invasive means of introducing nucleotides (e.g., injection) poses problems of tissue trauma (particularly in long-term therapies) and presents limited access to certain target tissues, such as organs.

Means for non-invasive delivery of pharmaceutical preparations of peptides, such as iontophoresis and other means for transdermal transmission, have the advantage of minimizing tissue trauma. However, it is believed that the bioavailability of peptides following transdermal or mucosal transmission is limited by the relatively high concentration of proteases in these tissues.

Injection of "naked DNA" directly into muscle has also been investigated at length. In 1984, work at the NIH was reported which showed that intrahepatic injection of naked, cloned plasmid DNA for squirrel hepatitis into squirrels produced both viral infection and the formation of antiviral antibodies in the squirrels (Seeger, et al, Proc.Nat'l.Acad.Sci USA, 81:5849–5852, 1984). Several years later, Felgner, et al., reported that they obtained expression of protein from "naked" polynucleotides (i.e., DNA or RNA not associated with liposomes or a viral expression vector) injected into skeletal muscle tissue (Felgner, et al., Science, 247:1465, 1990; see also, PCT application WO 90/11092). Feigner, et al. surmised that muscle cells efficiently take up and express

polynucleotides because of the unique structure of muscle tissue, which is comprised of multinucleated cells, sarcoplasmic reticulum and a transverse tubular system which extends deep into the muscle cell.

Today, injection of heterologous nucleic acid into cells of striated muscle is generally considered effective to cause expression of DNA or RNA injected into the cells. Gene transfer by injection into subjects of live cells containing nucleic acids that will express therapeutic genes in vivo is also greatly desired, particularly for treatment sites located within a body cavity that can be reached in a relatively noninvasive manner by the use of a catheter. However, gene transfer by injection of nucleic acid or cells containing therapeutic genes is complicated when the injection site is both remote (i.e., located within a body cavity) and in motion. A particularly difficult target for such therapeutic techniques is a beating heart and associated arterial tissue.

Further, even though the amount of the particular isolated therapeutic genes or cells injected into a patient is small, the costs involved in preparation of such therapeutic substances is high. Therefore, any injectate lost during transfer to the patient, for example, by leakage due to too rapid a transfer, represents a considerable monetary loss.

Accordingly, there is still a need in the art for new and better needles and injection systems or surgical assemblages suitable for microinjection of controlled amounts of therapeutic substances without substantial loss of injectate and without substantial damage to tissue, even upon repeat injections. There is a particular need for needles that are adapted for attachment to various types of catheters for such controlled delivery of therapeutic substances at remote locations within the body.

BRIEF DESCRIPTION OF THE INVENTION

The present invention overcomes many of the problems in the art by providing a surgical needle with a weeping tip for microinjection of medicaments into a body surface. The invention surgical needle comprises a nonporous hollow needle shaft having a proximal end adapted to mate with a surgical instrument, a porous distal portion in fluid-tight connection to the needle shaft, and a point that is open, closed or has a solid partial plug. The porous distal portion of the invention needle is adapted to cause a liquid injectate to weep or ooze therefrom multidirectionally under injection pressure while the distal portion and point of the needle are inserted into a body surface. Preferably, the invention needle has features that create a substantially uniform rate of weeping of injectate along the length of the porous distal portion thereof.

The invention surgical needle with weeping tip can be adapted for attachment to such surgical instruments as a syringe, but is preferably adapted for attachment to the distal tip of a catheter.

In another embodiment according to the present invention, there are provided surgical assemblage(s) useful for injecting a liquid medicament into a remote location in a subject in need thereof. The invention surgical assemblage comprises a needle with a sharp distal point with or without flow-through, and a catheter with a porous distal portion (such as a porous polymer) attached to the distal end of the needle, wherein the porous distal portion of the catheter is adapted to cause a liquid injectate to weep or ooze multidirectionally therefrom into surrounding tissue under injection pressure while inserted into a body surface. The remainder of the catheter is nonporous to assure that the medicament will be delivered only to tissue in contact with the porous portion of the catheter.

The invention surgical needle and/or surgical assemblage is ideally suited for injection into tissue of medicaments containing nucleic acid encoding a therapeutic agent (or cells containing such nucleic acid). For example, the invention needle (when attached to an appropriate catheter) or invention surgical assemblage can be used to inject medicament(s) into the wall of a beating heart or other internal organ, without substantial loss of the medicament at the surface of the body wall and without substantial damage to tissue at the injection site caused by injectate.

Accordingly, in another embodiment according to the present invention, there are provided methods for injecting a medicament into tissue in a subject in need thereof. The invention injection method comprises inserting the distal portion of the invention needle into the tissue of the subject and causing a therapeutic amount of the medicament to ooze multidirectionally from the needle into the tissue without substantial leakage or loss of the medicament at the surface of the tissue. The invention method using the invention needle (or surgical assemblage) with porous distal portion is designed for injection of minute amounts of fluid into tissue or a body wall, hence the use of the term "microinjection" herein.

In another embodiment according to the present invention, there are provided methods for injecting a medicament into a subject in need thereof comprising inserting the distal portion of the invention needle into an interior body wall or tissue of the subject and applying sufficient pressure to a liquid medicament in fluid communication with the distal portion of the needle to expel the medicament such that the medicament weeps multidirectionally from the pores in the distal portion thereof into the interior body wall or tissue without substantial leakage or loss of the medicament at the surface of the body wall. The invention methods are particularly useful for injecting medicament(s) into an interior body wall or tissue that is subject to motion, for example, the wall of a beating heart during electrophysiologic testing, transmyocardial revascularization, and the like.

In yet another embodiment, the present invention provides a method for injecting a medicament into tissue in a subject in need thereof comprising: inserting the distal portion of an invention needle into the tissue of the subject and causing a therapeutic amount of the medicament to ooze multidirectionally from the needle into the tissue without substantial damage to the tissue of the subject caused by injectate.

It is a particular object of the present invention to provide devices and methods useful for simultaneously injecting a medicament from multiple orifices along an injection course, rather than delivering a bolus injection, as is the case with traditional hypodermic needles.

BRIEF DESCRIPTION OF THE FIGURE

FIG. **1** is a schematic drawing showing an exploded view of the invention needle with weeping tip and a catheter to which it attaches.

FIG. **2** is a schematic drawing showing the invention needle with the electrical connector for attachment to an electrocardiogram.

FIG. **3** is a schematic drawing showing the invention surgical assemblage comprising a catheter and a needle, wherein the porous distal portion is located in the flexible catheter.

DETAILED DESCRIPTION OF THE INVENTION

The present invention overcomes many of the problems in the art by providing a surgical needle with a weeping tip for microinjection of medicaments into a body surface. The invention surgical needle comprises a nonporous hollow needle shaft having a proximal end adapted to mate with a surgical instrument, a porous distal portion in fluid-tight connection to the needle shaft, and a point that is open, closed, or has a solid partial plug. The distal portion of the invention needle is adapted to cause a liquid injectate to weep or ooze therefrom multidirectionally under injection pressure while the distal portion and point of the needle are inserted into a body surface. Typically, the length of the porous distal portion of the needle is determined by its intended use (e.g., whether intended for injecting medicament into a blood vessel or into a kidney, and the like). However, the porous distal portion is generally about 1 mm to about 20 mm in length and has pores with an average largest dimension in the range from about 1.0 micron to about 200 microns, for example, in the range from about 3 microns to about 100 microns, or from about 5 microns to about 75 microns.

The invention surgical needle with weeping tip can be adapted for attachment to such surgical instruments as a syringe, but is preferably adapted for attachment to the distal tip of a nonporous catheter. The assemblage of the needle and catheter is preferably steerable. For example, the needle can be attached to the distal tip of a steerable catheter (i.e., comprising a steering mechanism at the handle for controlling deflection of the distal tip section of the catheter shaft), such as is known in the art for injection of medicaments into a remote body cavity or organ wall. Alternatively, the needle can be attached to a catheter with a porous distal portion and then the combination can be introduced into a steerable guidance catheter, such as is used in such surgical techniques as angioplasty, transmyocardial revascularization (TMR), percutaneous transmyocardial revascularization (PTMR), and the like, to direct the needle and catheter to the appropriate site for injection of a medicament. Guidance catheters suitable for use in the invention assemblages and methods are commercially available, for example from such vendors as Eclipse Surgical Technologies (Sunnyvale, Calif.) and CardioGenesis Corp. (Sunnyvale, Calif.).

In one embodiment according to the present invention, the surgical needle is fabricated from a metal commonly used to make surgical needles, such as stainless steel, nitinol, tantalum, elgiloy, and the like, and provided with a distal portion having a multiplicity of pores, while the proximal portion of the needle (i.e., the nonporous hollow needle shaft) is fluid-tight to prevent leakage of fluid therefrom. Consequently, in use it is important to insert the complete porous distal portion of the needle into tissue before and during injection of a medicament.

In another embodiment according to the present invention, the porous distal portion of the surgical needle is adapted to create decreasing hydraulic impedance on injectate moving therethrough towards the point to cause a substantially uniform rate of weeping of injectate from the porous distal portion along the length thereof. The decrease in hydraulic impedance can be of any type, for example, linear, exponential, Gaussian, and the like, and with a gradient in either longitudinal direction.

For example, to create decreasing hydraulic impedance along the length of the porous portion, the size and/or number of the pores in the porous distal portion can increase along its length from the proximal end towards the point. Adjustment of the porosity along the length of the porous distal portion may also be in conjunction with an increasing interior diameter along the length of the porous portion from the proximal end towards the point as needed to offset a

falling off of injection pressure on fluid exiting towards the distal end of the device. Alternatively, if a different gradient of injectate is desired, the pore number and/or size can be arranged in any direction suitable to accomplish such a gradient.

The sharp point of the invention needle can be open, closed, or fitted with a solid partial plug to prevent the injectate from exiting as a single jet. If the point of the needle is open, the rate of flow from the open point can also be controlled by adjustment of the hydraulic impedance along the length of the distal portion of the needle to prevent the rate of fluid flow at the tip from substantially exceeding the rate of fluid flow along the porous portion adjacent to the point of the needle.

Alternatively, the point of the needle can be open, but restricted by a solid partial plug so that the distal tip of the needle is designed to operate similarly to the tip of a garden nozzle wherein the solid partial plug cooperates with the open tip to restrict exit of fluid, thereby preventing exit of the fluid as a single jet.

In another embodiment wherein the needle has an open tip, the tip (and a distal portion of the needle shaft) can be loosely covered or loosely sheathed with a porous material, such as the porous sintered metal mesh described above to create the porous distal portion of the needle. In this embodiment, the sheath is attached (e.g., fused or welded) to the needle shaft to create the porous portion from which injectate will weep or ooze (i.e., from the pores in the porous sheath).

The proximal end of the invention needle shaft is provided with a connector, such as a flange, hub, or the like, as is known in the art, for removable attachment of the needle to a surgical instrument, such as a syringe or a catheter. The surgical instrument serves as a reservoir for the fluid medicament. Therefore, the connector is such that there is fluid communication between the needle and the surgical instrument. In use, the invention needle is mounted on the distal tip of the surgical instrument, which is adapted to apply or transmit pressure to the medicament within the nonporous hollow shaft of the needle.

The distal portion of the needle can be fabricated from any of a number of different "open cell" porous materials (i.e., materials in which the pores are interconnecting). For example, the distal portion can be fabricated from a porous sintered metal, such as forms a non-woven matrix of metal fibers selected from such metals as stainless steel, tantalum, elgiloy, nitinol, and the like, and suitable combinations of any two or more thereof. Generally, the metal fibers will have a diameter in the range from about 1.0 micron to about 25 microns. A non-woven matrix of metal fibers having these desired properties that can be used in manufacture of the porous distal portion of the invention needle is available from the Bekaeart Corporation (Marietta, Ga.), and is sold under the trademark, BEKIPOR® filter medium.

The distal porous portion of the needle can also be fabricated from such porous materials as a porous polymer, such as a porous polyimide, polyethylene, polypropylene, polytetrafluroethylene, and the like. Such porous polymers are disclosed, for example, in U.S. Pat. No. 5,913,856, which is incorporated herein by reference in its entirety. Alternatively, a porous ceramic can be used, such as is known in the art for use in ceramic filters and separation membranes, or a porous metal (also known as an expanded metal) or carbon, such as is known in the art for use in filters or bone grafts. For example, Mott Corporation (Farmington, Conn.) manufactures porous metals for use in various types of filters.

If the porous filter medium is flexible, the distal portion of the invention needle can be fabricated by wrapping the filter medium, which is available commercially as a flat sheet, one or more times around an axis while creating a hollow central core. The porous distal portion of the needle can then be fused in fluid-tight fashion (e.g. welded) to a non-porous hollow needle shaft using methods known in the art. To create a porous portion of the needle having decreasing impedance to fluid flow, a porous filter medium or metal mesh having an appropriate porosity gradient can be employed in fabrication of the porous portion.

Alternatively, a porous distal portion for the invention needle can be created from a non-porous material (e.g., a metal) using a cutting laser and techniques known in the art to punch pores into the needle segment (i.e. by a process of laser etching). For example, the nonporous hollow shaft, porous portion, and point of the invention needle can be fabricated of metal in a single piece, for example, from a conventional hypotube. In this scenario, a metal-cutting laser is used to create a segment of the needle that has appropriate porosity, for example, a porosity gradient within a portion of the needle as disclosed herein to equalize fluid impedance along the length of the porous portion of the needle.

In any event, the porosity of the distal portion is generally in the range from about 50% to about 85%, for example, at least about 70%.

Thus, the multidirectional flow of medicament from the needle is controlled by a number of factors, for example, the size, multiplicity and arrangement of the pores in the distal portion, the viscosity of the liquid medicament, the pressure applied to the medicament via the surgical instrument to which it is attached (i.e., the "injection pressure"), and the like. Those of skill in the art will know how to select and combine these factors to assure that the medicament weeps multidirectionally from the pores in the distal portion of the needle into tissue into which it is inserted without substantial surface leakage or tissue damage attributable to the injectate. For example, by balancing these factors, the flow of a liquid medicament from the needle can be adjusted to be at a rate slow enough for the injectate to be absorbed into tissue in the injection site without substantial disruption of cellular and membrane structures as would be caused by bolus or rapid injection, especially from a needle having a single opening. A rate of injection in the range from about 0.1 cc per second to about 2.0 cc per second, for example, from about 0.5 cc per second to about 1.0 cc per second is generally suitable to accomplish these goals.

In the embodiment of the invention illustrated in FIG. **1** herein, needle **2** has a nonporous hollow needle shaft, a porous distal portion **6** having inter-connecting pores and a closed sharp tip **8**. Injectate **12** oozes from the pores in the distal portion under injection pressure. The sharp tip **8** of needle **2** is closed so that no injectate flows from the point of the needle. The proximal end of needle **2** is fitted with flange **10** for removable attachment to a catheter. The distal end of catheter **16**, which has at least one open lumen **14** for passage of injectate into needle **2** attaches to the proximal end of needle **2**. In other embodiments, a hub for mating with a syringe is substituted for the flange at the proximal end of the needle.

In another embodiment according to the present invention, the invention needle further comprises one or more sensor connectors for electrical attachment to an electrocardiogram. The electrocardiogram can be used to determine contact between the needle tip and the tissue, or

if multiple electrodes are present, to determine the depth of penetration. In the embodiment shown in FIG. **2**, the exterior of the needle shaft (not visible in this Figure) is coated with an insulator **18** and the connector **19** is attached directly to the proximal end (uncoated) of the needle shaft. Electrical lead **20** can be threaded down the lumen of a catheter for attachment to an electrocardiogram. Multiple leads can also be used in order to determine depth of the needle. In this configuration, the electrocardiogram is recorded from all leads. The larger signal is present from those ECG leads that are intramyocardial. Alternatively, the connector can be attached to the interior of the tip of the needle with an insulated connecting wire running down the hollow interior of the needle and catheter for attachment to an electrocardiogram. In this embodiment the needle itself acts as the electrode for the electrocardiogram and can be used for monopolar sensing of electrical currents or impedance within the heart, brain, nerves, proximal arteries, and the like.

For bipolar sensing a return electrode can be provided by placing an ECG pad in electrical connection with the electrocardiogram on the exterior of the patient, for example on the exterior of the chest wall. It is also contemplated within the scope of the invention that a second electrode or sensor connector can be attached to the needle, for example to the exterior of the needle, spaced apart from the first electrode by at least about 0.5 mm, so as to provide two electrodes for sensing electrical currents within a subject's bodily organs. It is also possible that an electrode permanently implanted in a subject, such as belongs to a pacemaker, can be used as the return lead for remote bipolar sensing.

The advantages of using the invention needles to perform sensing are several. For example, for injection into a muscle or other organ that has electrical impulses running through it, an electrocardiogram sensor attached to the invention needle can be used to confirm contact of the needle tip or proper insertion of the needle into the body wall of interest (e.g., the wall of a beating heart) before injection of the medicament into a treatment site. The depth of needle insertion into the tissue is determined by an array of electrodes. Those of skill in the art will realize that the invention needle having attached electrocardiogram sensor can also be used to judge whether such a prospective injection site is electrically active or not (i.e., whether the tissue is dead, hibernating due to lack of oxygen, or alive), and the like.

In another embodiment according to the present invention, there are provided surgical assemblages useful for microinjection of a liquid medicament into a remote location in a subject in need thereof. The invention surgical assemblage comprises a needle with a sharp distal point, and a catheter with a porous distal portion attached to the distal end of the needle, wherein the porous distal portion is adapted to cause a liquid injectate to weep or ooze multidirectionally therefrom into surrounding tissue under injection pressure while the porous distal portion of the catheter is inserted into a body surface. The catheter in the invention surgical assemblage can be a steerable catheter having a steering mechanism at the handle for controlling deflection of the distal tip section of the catheter shaft, thereby, in effect, creating a "steerable needle."

Alternatively, the invention surgical assemblage can further comprise a guidance catheter of the type known in the art for guiding instruments used in angioplasty, as is described more fully hereinabove. In this embodiment, the needle and catheter with porous distal portion is introduced into (i.e., threaded through) the guidance catheter so that the needle and catheter with porous distal portion can be directed to the site of injection (e.g., threaded through a desired section of tissue) using the steerable guidance catheter.

Preferably, the porous distal portion of the catheter is made of a flexible porous polymer, such as a porous polyimide, polyethylene, polytetrafluoroethylene, or polypropylene, and the like. The porous distal portion may further have features that create increasing hydraulic impedance on injectate moving therethrough towards the needle, thereby causing uniform flow of the injectate therefrom along the length of the porous distal portion as the injectate moves therethrough towards the needle to offset the falling off of injection pressure on fluid as it moves towards the point of the device. The flexibility of the porous segment in the assemblage facilitates injection of medicaments along a non-linear path.

As with the porous portion of the invention surgical needle described above, the size, and/or number of pores in the porous portion of the catheter in the invention surgical assemblage can be selected to create any desired gradient of injectate along the course of the injection path. For example, the size, and/or number of pores can decrease along the length of the porous portion moving towards the connection with the needle to allow for a substantially uniform rate of injectate weepage along the length of the porous portion. In this configuration, therefore, once the needle is used to thread the porous portion of the catheter through the tissue to be treated, a substantially uniform rate of fluid weepage into surrounding tissues can be obtained along the injection course. Alternatively, or in conjunction with such a porosity gradient, the porous distal portion can also have a decreasing interior diameter along its length moving from the proximal end towards the connection with the needle to accomplish the same goal.

FIG. **3** herein illustrates the invention surgical assemblage **22**. Non-porous needle **24** with a closed tip is attached to the distal end of flexible catheter **26**, which has a porous distal portion **28**. Injectate **30** weeps from the pores in the flexible distal portion **28** of catheter **26**.

In another embodiment according to the present invention, there are provided methods for injecting a medicament into an body wall in a subject in need thereof The invention method comprises inserting the porous distal portion of the invention needle into the tissue of the subject and applying sufficient injection pressure to a liquid medicament in fluid communication with the porous distal portion of the needle to cause the medicament to ooze multidirectionally from the pores in the needle into the tissue. Alternatively, the invention surgical assembly, wherein the porous portion is not contained in the needle, but is a porous distal portion of an otherwise nonporous catheter, can be used in the invention injection methods to similar effect. If the point and porous portion of the needle or surgical assembly are inserted into the tissue before the medicament is injected, the injection of medicament is performed without substantial leakage or loss of medicament at the surface of the tissue or interior body wall.

As used herein, the term "medicament(s)" includes all types of liquid substances (e.g., including solutions and suspensions) that have a beneficial or therapeutic effect. Non-limiting examples of medicaments suitable for use in the invention methods include biologically active agents, such as small molecule drugs, proteinaceous substances, polynucleotides or nucleic acids (e.g. heterologous DNA, or RNA) and vectors, liposomes, and the like, containing such nucleic acids or polynucleotides, as well as liquid preparations or formulations thereof.

The invention methods and devices are designed for injection of minute amounts of fluid medicaments into tissue or a body wall, for example, an interior body wall. Hence the use of the term "microinjection" herein. For example, the therapeutic amount of the medicament to be administered according to the invention method will vary depending upon the therapeutic goal to be accomplished, the size and age of the subject, the pharmacokinetics of the injectate, and the like. However, a therapeutic amount according to the present invention is typically in the range from about 0.5 cc to about 2.0 cc.

Under injection pressure exerted upon a fluid medicament within the invention needle or surgical assemblage, the injectate will weep or ooze multidirectionally from the porous distal portion into surrounding tissue into which it is inserted, but should be prevented from exiting from the proximal portions of the invention devices. Flow of the injectate into the surrounding tissue is contemplated to be at a slow rate, for example, in the range from about 0.1 cc per second to about 2.0 cc per second to allow absorption of and dissipation the medicament into the tissue without substantial tissue damage caused by the injectate, (e.g., pooling of the medicament is thereby avoided). So long as the injectate contains no particles (e.g. cells) larger than the pores in the distal portion of the needle, overall flow of the medicament into tissue will be proportional to the amount of pressure applied on the injectate.

However, unless the porous portion of the invention device is adapted to cause a increasing gradient of impedance to fluid flow as the fluid moves distally through the porous portion (i.e., towards the point of the needle), the medicament will not weep at a uniform flow rate along the length of the porous portion.

In practice of the invention methods, it is presently preferred that the combination of the needle and the surgical instrument to which it is attached be selected so that the amount of the medicament that oozes from the pores of the needle can be controlled by the operator. For example, if a measured amount of the medicament is placed for delivery into a calibrated chamber of the surgical instrument and/or hollow of the needle, pressure on the medicament in the chamber sufficient to deliver 2 cc of the medicament from the pores of the distal portion of the needle while the distal portion is inserted into tissue of the subject will substantially assure that the subject receives 2 cc of the medicament. This feature of the invention devices and methods is particularly advantageous when it is important to closely monitor the amount of the medicament delivered to the subject, for example, to avoid waste of the medicament, to accurately judge the efficacy of the treatment, and the like.

The invention methods can be used to deliver to a subject in need of gene therapy an therapeutic amount of a medicament containing an isolated therapeutic nucleic acid sequence, or a vector, liposome, or cell, and the like, containing such a nucleic acid sequence operatively associated with regulatory nucleic acid for expression of the encoded therapeutic protein. The invention devices and methods can be used to promote gene therapy by injection of such medicaments even when the injection site is located internally and/or is in constant motion. Therefore, in another embodiment according to the present invention, there are provided methods for injecting a therapeutic amount of a medicament into an interior body wall or tissue of a subject in need thereof. In this embodiment, the invention method comprises inserting the distal portion of the invention needle into an interior body wall or tissue of the subject and applying sufficient pressure to a liquid medicament in fluid communication with the distal portion of the needle to expel a therapeutic amount of the medicament such that the medicament weeps multidirectionally from the pores in the distal portion thereof into the interior body wall or tissue without substantial leakage or loss of the medicament at the surface of the body wall. The body wall can be located within a natural body cavity or a surgically created opening.

The invention method utilizing the needle with weeping tip is particularly useful for injection of medicaments into the wall of an interior organ that is subject to motion during the injection procedure, for example, the wall of a beating heart or adjacent arterial walls during electrophysiologic testing, transmyocardial revascularization, and the like. Additional internal organs subject to movement into which injections can be made using the invention methods include the stomach, esophagus, gallbladder, liver, bowel, kidney, lung, and the like.

By "isolated polynucleotide" or "isolated nucleic acid" or isolated nucleic acid sequence" is meant a polynucleotide that is not immediately contiguous with both of the coding sequences with which it is immediately contiguous (one on the 5' end and one on the 3' end) in the naturally occurring genome of the organism from which it is derived. The term therefore includes, for example, a recombinant DNA which is incorporated into a vector; into an autonomously replicating plasmid or virus; or into the genomic DNA of a prokaryote or eukaryote; or which exists as a separate molecule (e.g. a cDNA) independent of other sequences. Therapeutic nucleic acids contemplated for use in the practice of the present invention are intended to include those which encode products which are toxic to the cells in which they are expressed; those that encode products which impart a beneficial property to a subject; and those that transcribe nucleic acids which modulate transcription and/or translation of endogenous genes.

Preferred examples of suitable therapeutic nucleic acids for administration into cardiac tissues using the invention devices and methods include those encoding growth factors that enhance apoptosis and cell growth, such as bFGF (basic fibroblast growth factor, also known as FGF-2), AFGF (also known as FGF-1), EGF (epithelial growth factor), VEGF (vascular epithelial growth factor), angiostatin, ecchystatin, IGFs (insulin-like growth factors), and the like. These agents can be used to enhance or prevent the development of new blood vessels, prevent inflammation (as results from direct injection into the wall of an artery), prevent neointimal hyperplasia, or enhance or prevent the growth of new myocardial cells.

Additional therapeutic nucleic acids useful in the practice of the present invention include genes that encode biologically active proteins of interest, such as, e.g., secretory proteins that can be released from said cell; enzymes that can metabolize a toxic substance to produce a non-toxic substance, or that metabolize an inactive substance to produce a useful substance; regulatory proteins; cell surface receptors; and the like. Useful genes include genes that encode blood clotting factors, such as human factors VIII and IX; genes that encode hormones, such as insulin, parathyroid hormone, luteinizing hormone releasing factor (LHRH), alpha and beta seminal inhibins, and human growth hormone; genes that encode proteins, such as enzymes, the absence of which leads to the occurrence of an abnormal state; genes encoding cytokines or lymphokines such as interferons, granulocytic macrophage colony stimulating factor (GM-CSF), colony stimulating factor-1 (CSF-1), tumor necrosis factor (TNF), and erythropoietin (EPO); genes encoding inhibitor substances such as alphal-

antitrypsin; genes encoding substances that function as drugs, e.g., genes encoding the diphtheria and cholera toxins; and the like.

Typically, nucleic acid sequence information for proteins encoded by therapeutic nucleic acid(s) contemplated for use employed herein can be located in one of many public access databases, e.g., GENBANK, EMBL, Swiss-Prot, and PIR, or in related journal publications. Thus, those of skill in the art have access to sequence information for virtually all known genes. Those of skill in the art can obtain the corresponding nucleic acid molecule directly from a public depository or from the institution that published the sequence. Optionally, once the nucleic acid sequence encoding a desired protein has been ascertained, the skilled artisan can employ routine methods, e.g., polymerase chain reaction (PCR) amplification, to isolate the desired nucleic acid molecule from the appropriate nucleic acid library. Thus, all known nucleic acids encoding proteins of interest are available for use in the methods and products described herein.

Additional components that can optionally be incorporated into the invention constructs include selectable markers and genes encoding proteins required for retroviral packaging, e.g., the pol gene, the gag gene, the env gene, and the like.

Selectable markers contemplated for use in the practice of the present invention include antibiotic resistance genes, genes that enable cells to process metabolic intermediaries, and the like. Exemplary antibiotic resistance genes include genes which impart tetracycline resistance, genes that impart ampicillin resistance, neomycin resistance, hygromycin resistance, puromycin resistance, and the like.

Optionally, the cells can be obtained from the subject or host (i.e., rather than a donor), modified as above, and then reintroduced into the subject using the invention devices and methods. For example, therapeutic nucleic acid can be introduced directly into cells obtained from a subject and the modified cells can be then injected into the subject. The therapeutic nucleic acid may be stably incorporated into cells or may be transiently expressed using methods known in the art.

Modified cells are cultivated under growth conditions (as opposed to protein expression conditions) until a desired density is achieved. Stably transfected mammalian cells may be prepared by transfecting cells with an expression vector having a selectable marker gene (such as, for example, the gene for thymidine kinase, dihydrofolate reductase, neomycin resistance, and the like), and growing the transfected cells under conditions selective for cells expressing the marker gene. To prepare transient transfectants, mammalian cells are transfected with a reporter gene (such as the *E. coli* Bgalactosidase gene) to monitor transfection efficiency. Selectable marker genes are typically not included in the transient transfections because the transfectants are typically not grown under selective conditions, and are usually analyzed within a few days after transfection.

The concept of gene replacement therapy for humans involves the introduction of functionally active nucleic acids into the somatic cells of an affected subject to correct a gene defect or deficiency. Genes that encode useful "gene therapy" proteins that are not normally transported outside the cell can be used in the invention if such genes are "functionally appended" to, or operatively associated with, a signal sequence that can "transport" the encoded product across the cell membrane. A variety of such signal sequences are known and can be used by those skilled in the art without undue experimentation.

Regulatory elements employed in the practice of the present invention are operably linked to a suitable promoter for transcription of therapeutic nucleic acid product(s). As used herein, the term "promoter" refers to a specific nucleic acid sequence recognized by RNA polymerase, the enzyme that initiates RNA synthesis. The promoter sequence is the site at which transcription can be specifically initiated under proper conditions. When exogenous nucleic acid(s), operatively linked to a suitable promoter, are introduced into the cells of a suitable host, expression of the exogenous nucleic acid(s) can be controlled in many, but not all cases, by the presence of ligands, which are not normally present in the host cells.

Promoters contemplated for control of expression of exogenous nucleic acids employed in the practice of the present invention include inducible (e.g., minimal CMV promoter, minimal TK promoter, modified MMLV LTR), constitutive (e.g., chicken Pactin promoter, MMLV LTR (non-modified), DHFR), and/or tissue specific promoters.

Inducible promoters contemplated for use in the practice of the present invention comprise transcription regulatory regions that function maximally to promote transcription of mRNA under inducing conditions. Examples of suitable inducible promoters include DNA sequences corresponding to: the *E. coli* lac operator responsive to IPTG (see Nakamura et al., *Cell,* 18:1109–1117, 1979); the metallothionein promoter metal-regulatory-elements responsive to heavy-metal (e.g., zinc) induction (see Evans et al., U.S. Pat. No. 4,870,009), the phage T71ac promoter responsive to IPTG (see Studier et al., *Meth. Enzymol.,* 185: 60–89, 1990; and U.S. Pat. No. 4,952,496), the heat-shock promoter; the TK minimal promoter; the CMV minimal promoter; a synthetic promoter; and the like.

Exemplary constitutive promoters contemplated for use in the practice of the present invention include the CMV promoter, the SV40 promoter, the DHFR promoter, the mouse mammary tumor virus (MMTV) steroid-inducible promoter, Moloney murine leukemia virus (MMLV) promoter, elongation factor 1a (EF1a) promoter, albumin promoter, APO A1 promoter, cyclic AMP dependent kinase II (CaMKII) promoter, keratin promoter, CD3 promoter, immunoglobulin light or heavy chain promoters, neurofiliment promoter, neuron specific enolase promoter, L7 promoter, CD2 promoter, myosin light chain kinase promoter, HOX gene promoter, thymidine kinase (TK) promoter, RNA Pol II promoter, MYOD promoter, MYF5 promoter, phosphoglycerokinase (PGK) promoter, Stf1 promoter, Low Density Lipoprotein (LDL) promoter, chicken β-actin promoter (e.g., used in conjunction with an ecdysone response element), and the like.

As readily understood by those of skill in the art, the term "tissue specific" refers to the substantially exclusive initiation of transcription in the tissue from which a particular promoter that drives expression of a given gene is derived (e.g., expressed only in T-cells, endothelial cells, smooth muscle cells, and the like). Exemplary tissue specific promoters contemplated for use in the practice of the present invention include the GH promoter, the NSE promoter, the GFAP promoter, neurotransmitter promoters (e.g., tyrosine hydroxylase, TH, choline acetyltransferase, ChAT, and the like), promoters for neurotropic factors (e.g., a nerve growth factor promoter, NT-3, BDNF promoters, and the like), and so on.

As used herein, the phrase "operatively associated with" refers to the functional relationship of DNA with regulatory and effector sequences of nucleic acids, such as promoters,

enhancers, transcriptional and translational stop sites, and other signal sequences. For example, operative linkage of DNA to a promoter refers to the physical and functional relationship between the DNA and promoter such that the transcription of such DNA is initiated from the promoter by an RNA polymerase that specifically recognizes, binds to and transcribes the DNA.

Gene transfer vectors (also referred to as "expression vectors") contemplated for use herein are recombinant nucleic acid molecules that are used to transport nucleic acid into host cells for expression and/or replication thereof. Expression vectors may be either circular or linear, and are capable of incorporating a variety of nucleic acid constructs therein. Expression vectors typically come in the form of a plasmid that, upon introduction into an appropriate host cell, results in expression of the inserted nucleic acid.

Suitable expression vectors for use herein are well known to those of skill in the art and include recombinant DNA or RNA construct(s), such as plasmids, phage, recombinant virus or other vectors that, upon introduction into an appropriate host cell, result(s) in expression of the inserted DNA. Appropriate expression vectors are well known to those of skill in the art and include those that are replicable in eukaryotic cells and/or prokaryotic cells and those that remain episomal or those which integrate into the host cell genome. Expression vectors typically further contain other finctionally important nucleic acid sequences encoding antibiotic resistance proteins, and the like.

The amount of therapeutic nucleic acid introduced into a subject can be varied by those of skill in the art. For example, when a viral vector is employed to achieve gene transfer, the amount of nucleic acid introduced can be varied by varying the amount of plaque forming units (PFU) of the viral vector.

Exemplary eukaryotic expression vectors include eukaryotic constructs, such as the pSV-2 gpt system (Mulligan et al., *Nature* 277: 108–114, 1979); pBlueSkript (Stratagene, La Jolla, Calif.), the expression cloning vector described by Genetics Institute (*Science* 228:810–815, 1985), and the like. Each of these plasmid vectors is capable of promoting expression of the protein product of the nucleic acid of interest.

Suitable means for introducing (transducing) expression vectors containing therapeutic nucleic acid constructs into cells of a subject treated according to the invention methods include infection employing viral vectors (see, e.g., U.S. Pat. Nos. 4,405,712 and 4,650,764). The transduced nucleic acid can optionally include sequences which allow for its extrachromosomal (i.e., episomal) maintenance, or the transduced nucleic acid can be donor nucleic acid that integrates into the genome of the host.

In a specific embodiment, a gene transfer vector contemplated for use herein is a viral vector, such as Adenovirus, adeno-associated virus, a herpes-simplex virus based vector, a synthetic vector for gene therapy, and the like (see, e.g., Suhr et al., *Arch. of Neurol.* 50: 1252–1268, 1993). Preferably, a gene transfer vector employed herein is a retroviral vector. Retroviral vectors contemplated for use herein are gene transfer plasmids that have an expression construct containing an exogenous nucleic acid residing between two retroviral LTRs. Retroviral vectors typically contain appropriate packaging signals that enable the retroviral vector, or RNA transcribed using the retroviral vector as a template, to be packaged into a viral virion in an appropriate packaging cell line (see, e.g., U.S. Pat. No. 4,650,764).

Suitable retroviral vectors for use herein are described, for example, in U.S. Pat. Nos. 5,399,346 and 5,252,479; and in WIPO publications WO 92/07573, WO 90/06997, WO 89/05345, WO 92/05266 and WO 92/14829, each of which is hereby incorporated herein by reference, in its entirety. These documents provide a description of methods for efficiently introducing nucleic acids into human cells using such retroviral vectors. Other retroviral vectors include, for example, mouse mammary tumor virus vectors (e.g., Shackleford et al *PNAS, USA,* 85:9655–9659, 1988), human immunodeficiency virus (e.g., Naldini et al. *Science* 272:165–320, 1996), and the like.

Various procedures are also well-known in the art for providing helper cells which produce retroviral vector particles that are essentially free of replicating virus. See, for example, U.S. Pat. No. 4,650,764; Miller, *Human Gene Therapy,* 1:5–14, 1990; Markowitz, et al., *Journal of Virology,* 61(4): 120–1124, 1988; Watanabe, et al., *Molecular and Cellular Biology,* 3(12):2241–2249, 1983; Danos, et al., *PNAS,* 8:6460–6464, 1988; and Bosselman, et al., *Molecular and Cellular Biology,* 7(5):1797–1806, 1987, which disclose procedures for producing viral vectors and helper cells that minimize the chances for producing a viral vector that includes a replicating virus.

Recombinant retroviruses suitable for carrying out the invention methods are produced employing well-known methods for producing retroviral virions. See, for example, U.S. Pat. No. 4,650,764; Miller, supra 1990; Markowitz, et al., supra 1988; Watanabe, et al., supra 1983; Danos, et al., *PNAS,* 85:6460–6464, 1988; and Bosselman, et al., *Molecular and Cellular Biology,* 7(5)1797–1806, 1987.

By introducing all of the necessary regulatory machinery, plus exogenous nucleic acid, selectable markers, and nucleic acid encoding invention chimeric protein, e.g., into a MARV retrovirus, highly efficient insertion of exogenous nucleic acids into targeted cells can be achieved.

Thus, the above-described viral constructs address several important problems confronted in the use of retroviruses in application of therapeutic gene transfer strategies to a variety of human diseases. For example, the retroviral vectors of the invention are capable of prolonged gene expression under conditions where conventionally integrated retroviruses are no longer transcriptionally active.

As used herein, when referring to nucleic acids, the phrase "exogenous to said mammalian host" or simply "exogenous" refers to nucleic acids not naturally found at levels sufficient to provide a function in the particular cell where transcription is desired. For example, exogenous nucleic acids can be either natural or synthetic nucleic acids, which are introduced into the subject in the form of DNA or RNA. The nucleic acids of interest can be introduced directly or indirectly into a subject, for example, by the transfer of transformed cells into a subject using invention methods.

As employed herein, the terms "subject" and "host" refer to a mammalian patient in need of administration of a medicament. The subject mammals include: humans; domesticated animals, e.g., rat, mouse, rabbit, canine, feline, and the like; farm animals, e.g., chicken, bovine, ovine, porcine, and the like; animals of zoological interest, e.g., monkey, baboon, and the like.

While the invention has been described in detail with reference to certain preferred embodiments thereof, it will be understood that modifications and variations are within the spirit and scope of that which is described and claimed.

What is claimed is:

1. A surgical needle comprising:

a nonporous hollow needle shaft having a proximal end adapted to mate with a surgical instrument,

a porous distal portion in fluid-tight connection to the distal end of the needle shaft, and

a point that is open, closed, or has a solid partial plug,

wherein a gradient in the size or distribution of the pores and/or interior diameter of the porous distal portion causes a gradient of hydraulic impedance on a liquid injectate moving therethrough towards the point and

wherein the pores are sized to cause the injectate to weep or ooze therefrom multidirectionally under injection pressure while the point and distal portion of the needle are inserted into a body surface.

2. The needle according to claim 1 wherein the porous distal portion has pores with an average largest dimension in the range from about 1.0 micron to about 200 microns.

3. The needle according to claim 1 wherein the gradient is linear, exponential or Gaussian in either longitudinal direction.

4. The needle according to claim 1 wherein the gradient is a decreasing gradient.

5. The needle according to claim 1 wherein the porous distal portion has an increasing interior diameter along the length thereof from the proximal end to the point.

6. The needle according to claim 1 wherein the size and/or number of the pores in the porous distal portion increases along the length thereof from the proximal end to the point.

7. The needle according to claim 1 wherein at least the porous distal portion is fabricated from a porous carbon, metal, ceramic, or polymer.

8. The needle according to claim 7 wherein the porous distal portion is fabricated from a porous metal.

9. The needle according to claim 7 wherein the porous distal portion is fabricated from a porous polymer.

10. The needle according to claim 7 wherein the porous distal portion is fabricated from a porous carbon or ceramic.

11. The needle according to claim 1 wherein the porous distal portion has a porosity of about 50% to about 85%.

12. The needle according to claim 1 wherein flow of a liquid from the needle is in the range from about 0.1 cc/sec to about 2.0 cc/sec.

13. The needle according to claim 1 wherein the surgical instrument is a catheter.

14. The needle according to claim 13 wherein the catheter is a steerable endoscopic catheter.

15. The needle according to claim 1 wherein the surgical instrument is a syringe.

16. The needle according to claim 1 wherein the needle further comprises one or more connectors for electrical attachment to an electrocardiogram.

17. The needle according to claim 16 wherein the exterior of the needle shaft is coated with an insulator and the connector is electrically connected to the proximal end of the needle shaft.

18. A method for injecting a medicament into tissue in a subject in need thereof, said method comprising:

inserting the distal portion of the needle according to claim 1 into the tissue of the subject and causing a therapeutic amount of the medicament to ooze multidirectionally from the needle into the tissue without substantial leakage or loss of the medicament at the surface of the tissue.

19. The method according to claim 18 wherein the amount is from about 0.5 cc to about 2.0 cc of the medicament.

20. The method according to claim 18 wherein injection pressure is applied to the liquid medicament in fluid communication with the distal portion of the needle to cause a therapeutic amount of the medicament to ooze from the needle.

21. The method according to claim 18 wherein flow of the medicament from the needle is in the range from about 0.1 cc/sec to about 2.0 cc/sec.

22. The method according to claim 18 wherein the medicament comprises an isolated therapeutic nucleic acid sequence.

23. The method according to claim 22 wherein the nucleic acid sequence is contained within a vector, a liposome, or a cell.

24. A method for injecting a medicament into a subject in need thereof, said method comprising:

inserting the distal portion of the needle of claim 1 into an interior body wall or tissue of the subject and

applying sufficient pressure to a liquid medicament in fluid communication with the distal portion of the needle to expel the medicament,

whereby the medicament weeps multidirectionally from the pores in the distal portion into the interior body wall without substantial leakage or loss of the medicament at the surface of the tissue.

25. The method according to claim 24 wherein the needle has an increasing interior diameter along the length thereof from the proximal end to the point and the flow of the medicament into the surrounding tissue is substantially equal along the length of the porous distal portion of the needle.

26. The method according to claim 24 wherein the needle is attached to a syringe.

27. The method according to claim 24 wherein the needle is attached to the distal tip of a catheter and the body wall is within a body cavity.

28. The method according to claim 27 wherein the catheter is a steerable catheter that is used to guide the needle to an injection site.

29. The method according to claim 27 wherein a guidance catheter is used to guide the needle and catheter with porous distal portion to an injection site.

30. The method according to claim 27 wherein the body cavity is surgically created.

31. The method according to claim 27 wherein the body wall is subject to motion.

32. The method according to claim 31 wherein the body wall is in a beating heart.

33. The method according to claim 24 wherein the needle further comprises at least one sensor in electrical connection to an electrocardiogram and the method further comprises sensing electrical activity in the body wall.

34. The method according to claim 33 wherein electrical activity is sensed prior to injection of the medicament.

35. The method according to claim 33 wherein the needle comprises multiple sensors and wherein the multiple sensors are used to determine the depth of needle penetration into the tissue of the subject before, during and/or after the injection of medicament.

36. The method according to claim 24 wherein the body wall is in a beating heart.

37. The method according to claim 24 wherein the body wall is within an artery.

38. The method according to claim 24 wherein the medicament comprises a isolated therapeutic nucleic acid sequence.

39. The method according to claim 38 wherein the nucleic acid sequence is contained within a vector, liposome, or cell.

40. The method according to claim **38** wherein the therapeutic nucleic acid sequence encodes bFGF, aFGF, EGF, VEGF, angiostatin, ecchystatin, or an IGF.

41. The method according to claim **40** wherein the therapeutic nucleic acid is contained within a viral vector.

42. The method according to claim **24** wherein the medicament comprises genetically engineered cells containing a isolated nucleic acid sequence that encodes a therapeutic gene product.

43. The method according to claim **39** wherein the cell is heterologous.

44. The method according to claim **38** wherein the cell is obtained from the subject.

* * * * *

United States Patent [19]

Rangaswamy

[11] **Patent Number: 4,512,768**

[45] **Date of Patent: Apr. 23, 1985**

[54] **ANALGESIC SYRINGE**

[76] Inventor: **Avvari Rangaswamy**, Stevens Hospital, Welch, W. Va. 24801

[21] Appl. No.: **466,535**

[22] Filed: **Feb. 15, 1983**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 417,188, Sep. 10, 1982, abandoned.

[51] **Int. Cl.**[3] **A61M 5/00**

[52] **U.S. Cl.** **604/191**; 604/272

[58] **Field of Search** 604/88, 89, 90, 190, 604/191, 164, 272

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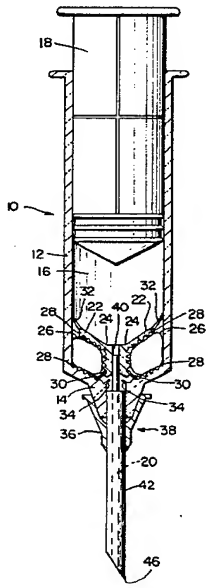
Primary Examiner—John D. Yasko

Attorney, Agent, or Firm—Memel, Jacobs, Pierno & Gersh

[57] **ABSTRACT**

A syringe article, for analgesic puncture with twin needles, the syringe containing a thin walled plastic reservoir filled with local anesthetic mounted under a collapsible roof and located at the distal end of the syringe barrel adjacent the twin needles, so that depression of the syringe plunger compresses sharp projections against the reservoir which is then ruptured to release the local anesthetic for injection into the flesh which will be punctured, the local anesthetic being passed through pores in the wall of an outer positioned needle into the patient's flesh.

5 Claims, 5 Drawing Figures



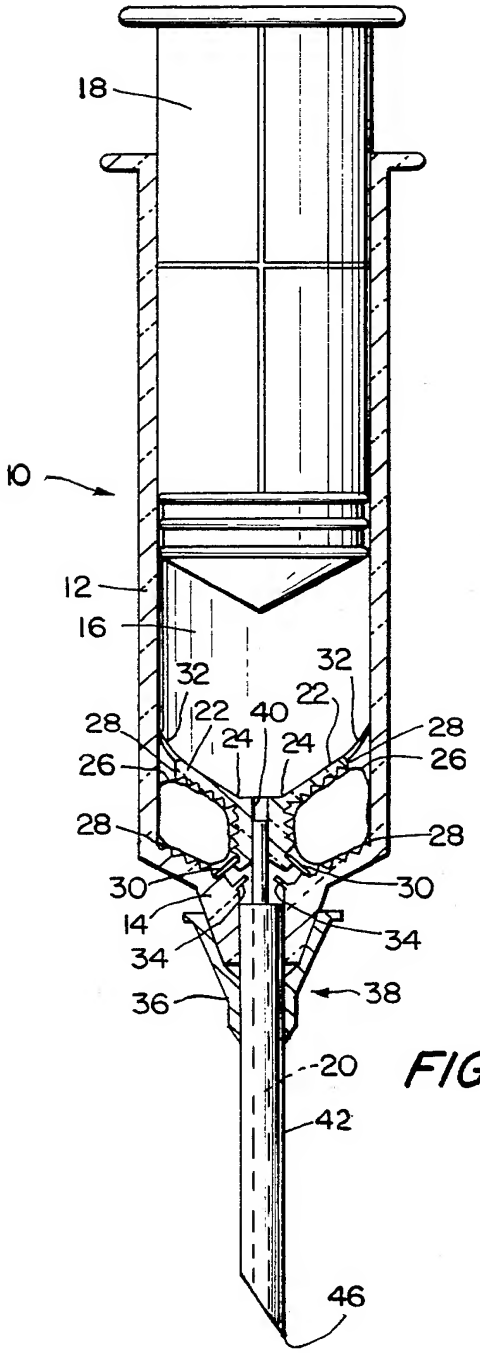

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FIG. 1

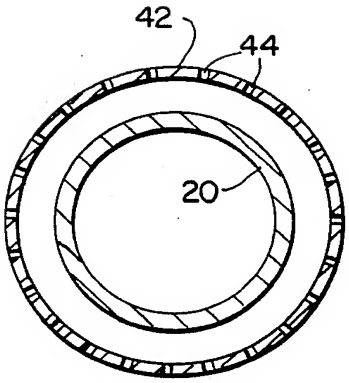
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FIG. 2

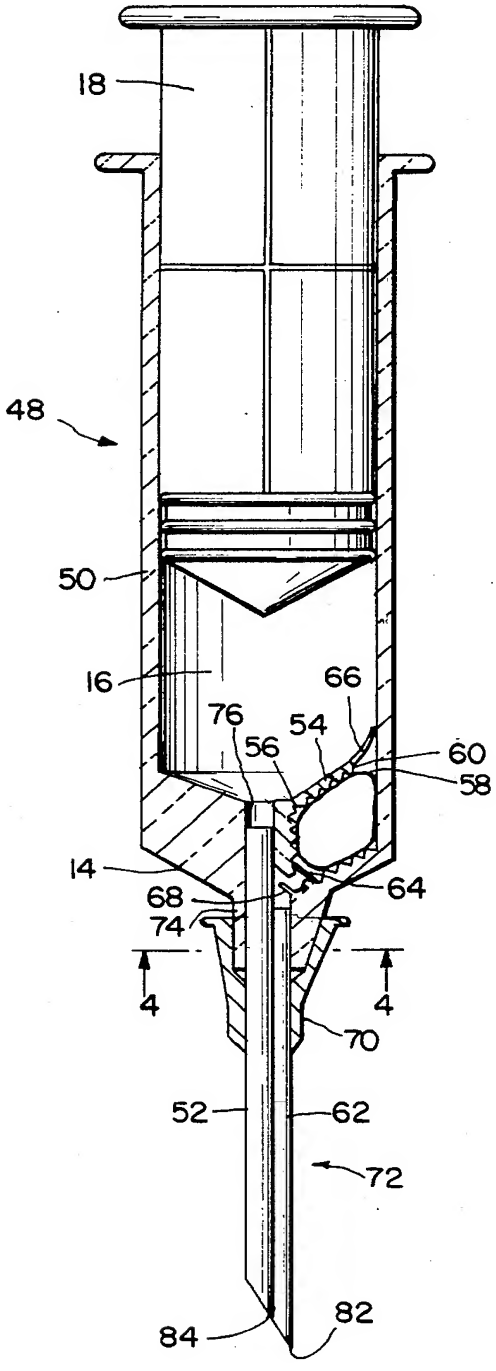

FIG. 3

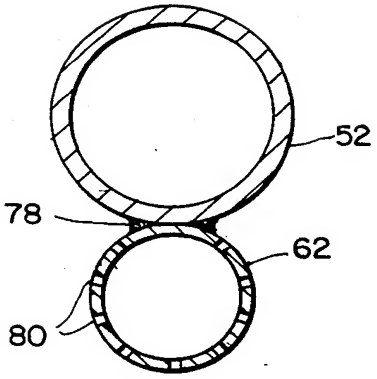

FIG. 5

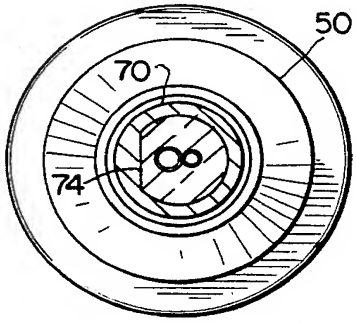

FIG. 4

ANALGESIC SYRINGE

BACKGROUND OF THE INVENTION

This application is a continuation-in-part of application Ser. No. 417,188 of Avvari Rangaswamy filed Sept. 10, 1982 now abandoned.

This invention relates to syringes for painlessly performing a venipuncture or similar puncture type procedure, and, more particularly, to syringes which provide for multi-directional initial injection of a local anesthetic so as to allow for painless passage of a needle into a patient.

Various syringe types are known in the art which provide for multi-medication injections. In general, these syringes incorporate moveable seals in the cylinder of the syringe so that various pharmaceutical substances can be separately contained in the syringe for serial injection. As the plungers of such syringes are depressed into the syringe cylinders the moveable seals advance the various preloaded pharmaceuticals toward the syringe needle. The succeeding pharmaceuticals, after the first is passed through the syringe needle, are fed into the needle by having an extension of the needle, into the cavity of the syringe cylinder, pierce through the moveable seals as they are advanced by the plunger. However, because the pharmaceuticals only pass into the patient through a single exit located at end of needle, all such known multi-medication syringe types are incapable of providing effective precursor local anesthetization for the passage of the syringe needle into a patient.

SUMMARY OF THE INVENTION

Venipuncture is one of the more commonly performed medical procedures. Such surgical puncture of a vein to either withdraw fluid or insert a needle, with or without a soft intravenous catheter, to administer intravenous fluids can be a difficult and painful procedure for many patients—especially for children or the frequently hospitalized patients in whom it can be difficult to insert a large bore needle into a vein. The present invention minimizes the discomfort associated with such procedures, and is particularly useful in treating children and patients in whom it is hard to find a moderate size vein.

This invention consists of a syringe with a thin walled plastic reservoir lodged under a collapsible roof that is located at the distal end of the syringe barrel adjacent the needle. Hermetically stored in the thin walled reservoir is a local anesthetic. Depression of the syringe plunger applies pressure to the collapsible roof which compresses sharp projections through the walls of the plastic reservoir. The sharp projections rupture the plastic reservoir, and the continued depression of the plunger induces flow of the anesthetic through a filter and one way valve into a porous needle. The porous needle projects forward of a second needle. This second needle is coupled to the syringe cylinder for passage of fluids. The openings along the length of the porous needle provide for flow of the local anesthetic in multiple directions which results in anesthetization of the region through which the needles are passed in search of a vein or body cavity.

BRIEF DESCRIPTION OF THE DRAWINGS

In the drawings:

FIG. 1 is a partial cross section of a syringe with an aqueduct needle according to the present invention;

FIG. 2 is a further cross section of the aqueduct needle illustrated in FIG. 1;

FIG. 3 is a partial cross section of a syringe with a paired needle structure according to the present invention;

FIG. 4 is a cross section of the distal end of the syringe illustrated in FIG. 3 showing how the paired needle structure is registered to fit into the syringe barrel; and,

FIG. 5 is a further cross section of the paired needle structure illustrated in FIG. 3.

DETAILED DESCRIPTION OF THE INVENTION

Referring now to the drawings, wherein corresponding components are designated by the same reference numerals throughout the various figures, a syringe according to the invention is illustrated in FIG. 1 and generally designated by reference numeral 10. Syringe 10 includes a syringe barrel 12 having a distal end 14. The syringe barrel 12 is fabricated of plastic. Within the syringe barrel 12 is a cylinder 16 into which can be inserted a plunger 18 for evacuating the hollow cylinder 16 through a continuous walled cannula 20.

At the distal end 14 of the syringe barrel 12 is an annular collapsible roof 22. The annular collapsible roof 22 is attached to the syringe barrel 12 by a flexible section 24 providing a hinge for the annular collapsible roof 22. Lodged within the distal end 14 of the syringe barrel 12 under the collapsible roof 22 is an annular thin walled plastic reservoir 26 which contains a local anesthetic. The local anesthetic is released from the reservoir 26, which is ruptured, when the annular collapsible roof 22 compresses sharp plastic projections 28 into the reservoir 26. After release from the reservoir 26 the local anesthetic flows through annular filter 30, which prevents plastic material from ruptured reservoir 26 passing into porous needle 42. Such a flow path for the local anesthetic is preferred because flow back into the hollow cylinder 16 is inhibited by the annular collapsible roof 22 with its continuous hinge 24 and pliable annular seal 32. After passage through the annular filter 30 the local anesthetic passes through an annular one way valve consisting of a flexibly hinged plastic seal 34 which is open when fluid pressure is applied as a result of the local anesthetic being released from the plastic reservoir 26. The hinged plastic seal 34 closes the one way valve when the ambient pressure on the opposite side of the hinged plastic seal 34 from the plastic reservoir 26 is greater than that produced by the annular collapsible roof 22 compressing the reservoir 26. Such closing of the one way valve by hinged plastic seal 34 prevents fluids from backing up into the plastic reservoir 26 region. An example of when such backing up of fluid could occur is when fluid is being withdrawn from a patient by syringe 10.

Affixed at the distal end 14 of syringe 10 by a hub 36 is an aqueduct needle 38. Tube 40 within the distal end 14 of syringe 10 provides a sealing fit for the continuous walled cannula 20 so that fluids can be either passed to or from hollow cylinder 16 through the continuous walled cannula 20 which has openings at both ends. Annularly surrounding continuous walled cannula 20 is a porous needle 42 which has pores 44 around (See FIG. 2) and substantially along its entire length from hub 36 to its end 46. These pores 44 are closely and

substantially uniformly spaced on the exterior wall of needle 42 so as to provide for uniform infusion of the local anesthetic from plastic reservoir 26 into the patient along the entire length of the aqueduct needle 38 which is inserted, and not just the end 46. Such uniform infusion assures effective anesthization for painless insertion of the aqueduct needle.

Another exemplary embodiment of the invention is shown in FIG. 3. Here syringe 48 includes a syringe barrel 50 having a distal end 14. The syringe barrel 50 is fabricated of plastic. Within the syringe barrel 50 is a hollow cylinder 16 into which can be inserted a plunger 18 for evacuation of the hollow cylinder 16 through a needle 52.

At the distal end 14 of the syringe barrel 50 is a collapsible roof 54. The collapsible roof 54 is attached to the syringe barrel 50 by a flexible section 56 providing a hinge for the collapsible roof 54. Lodged within the distal end 14 of the syringe barrel 50 under the collapsible roof 54 is a thin walled plastic reservoir 58 which contains a local anesthetic. The local anesthetic is released from the plastic reservoir 58, which is ruptured, when the collapsible roof 54 compresses sharp plastic projections 60 into the reservoir 58. After release from the reservoir 58 the local anesthetic flows through filter 64, which prevents plastic material from ruptured reservoir 58 passing into porous needle 62. Such a flow path for the local anesthetic is preferred because flow back into the hollow cylinder 16 is inhibited by the collapsible roof 54 with its continuous flexible hinge 56 and pliable seal 66. After passage through the filter 64 the local anesthetic passes through a one way valve consisting of a flexible hinged plastic seal 68 which is open when fluid pressure is applied as a result of the local anesthetic being released from the plastic reservoir 58. The hinged plastic seal 68 closes the one way valve when the ambient pressure on the opposite side of the hinged plastic seal 68 from the plastic reservoir 58 is greater than that produced by the collapsible roof 54 compressing the reservoir 58. Such closing of the one way valve by hinged plastic seal 68 prevents fluids from backing up into the plastic reservoir 58 region.

Affixed at the distal end 14 of syringe 48 by a hub 70 is a paired needle structure 72. Hub 70 is keyed for fitting onto syringe barrel 50 so that both needle 52 and porous needle 62 are rotationally properly aligned with syringe barrel 50. This registration of both needle 52 and porous needle 62 is accomplished by having a flat registration section 74 oriented with respect to both syringe barrel 50 and hub 70 that the paired needle structure 72 is properly aligned.

Tube 76 within the distal end 14 of syringe 48 provides a sealing fit for needle 52 so that fluids can be either passed to or from hollow cylinder 16 through needle 52. Abutting needle 52 and firmly affixed to it by a joint 78 is the narrow gauge (25–28G) porous needle 62. The narrow gauge porous needle 62 has pores 80 around (see FIG. 5) and substantially along its entire length from hub 70 to its end 82. These pores 80 are closely and substantially uniformly spaced on the exterior of porous needle 62 so as to provide for uniform infusion of the local anesthetic from plastic reservoir 58 into the patient along the entire length of the porous needle 62 which is inserted and not just the end 82. To further assure effective anesthization for painless insertion of the paired needle structure the narow gauge porous needle extends in front of the end 84 of needle 52 by 1/16th to 1/8th inch.

The above discussion and related illustrations of the present invention are directed primarily to preferred embodiments and practices of the invention. However, it is believed that numerous changes and modifications in the actual implementation of the concepts described herein will be apparent to those skilled in the art, and it is contemplated that such changes and modifications may be made without departing from the scope of the invention as defined by the following claims.

What is claimed is:

1. A syringe, comprising: means for releasing a first pharmaceutical into a porous needle as said porous needle is being inserted in a patient, and said porous needle being in fixed adjacent proximity with a continuous walled cannula or needle through which (1) a second pharmaceutical can be passed or (2) fluids can be withdrawn from the patient;

whereby said first pharmaceutical is infused substantially uniformly into the patient along the length of the inserted porous needle and therefore into the region which said continuous walled cannula or needle is passed.

2. A syringe as set forth in claim 1 in which said continuous walled cannula or needle is contained within said porous needle so that a fluid can be dispensed through the end and pores of said porous needle, and a separate fluid can be dispensed through the end of said continuous walled cannula or needle, or fluids can be withdrawn from the patient.

3. A syringe as set forth in claim 1 in which said continuous walled cannula or needle is abuttingly fixed longitudinally to said porous needle so that a fluid can be dispensed through the end and pores of said porous needle, and a separate fluid can be dispensed, or fluids can be withdrawn from the patient, through the end of said continuous walled cannula or needle.

4. A syringe as set forth in claim 1 in which said first pharmaceutical is contained in a hermetically sealed reservoir, which reservoir can be ruptured by means activated by depressing the syringe plunger so that said first pharmaceutical flows into said porous needle.

5. A syringe as set forth in claim 4 in which said first pharmaceutical flows from said ruptured reservoir through a filter and one way valve prior to entering said porous needle.

* * * * *

US006503225B1

(12) **United States Patent**
Kirsch et al.

(10) **Patent No.: US 6,503,225 B1**
(45) **Date of Patent: Jan. 7, 2003**

(54) **DEVICE FOR REMOVAL OF GAS BUBBLES AND DISSOLVED GASSES IN LIQUID**

(75) Inventors: **Claudia F. E. Kirsch**, New York, NY (US); **Bradley W. Reed**, Gastonia, NC (US)

(73) Assignee: **Celgard Inc.**, Charlotte, NC (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/530,309**

(22) PCT Filed: **Aug. 26, 1998**

(86) PCT No.: **PCT/US98/17718**

§ 371 (c)(1),
(2), (4) Date: **Oct. 23, 2000**

(87) PCT Pub. No.: **WO99/32186**

PCT Pub. Date: **Jul. 1, 1999**

Related U.S. Application Data

(63) Continuation of application No. 09/111,143, filed on Jul. 7, 1998, now abandoned.
(60) Provisional application No. 60/077,892, filed on Mar. 13, 1998, and provisional application No. 60/068,426, filed on Dec. 22, 1997.

(51) **Int. Cl.**[7] **A61M 1/00**
(52) **U.S. Cl.** **604/126**; 422/48
(58) **Field of Search** 604/118, 126; 96/8; 210/321.8, 645, 137; 422/48

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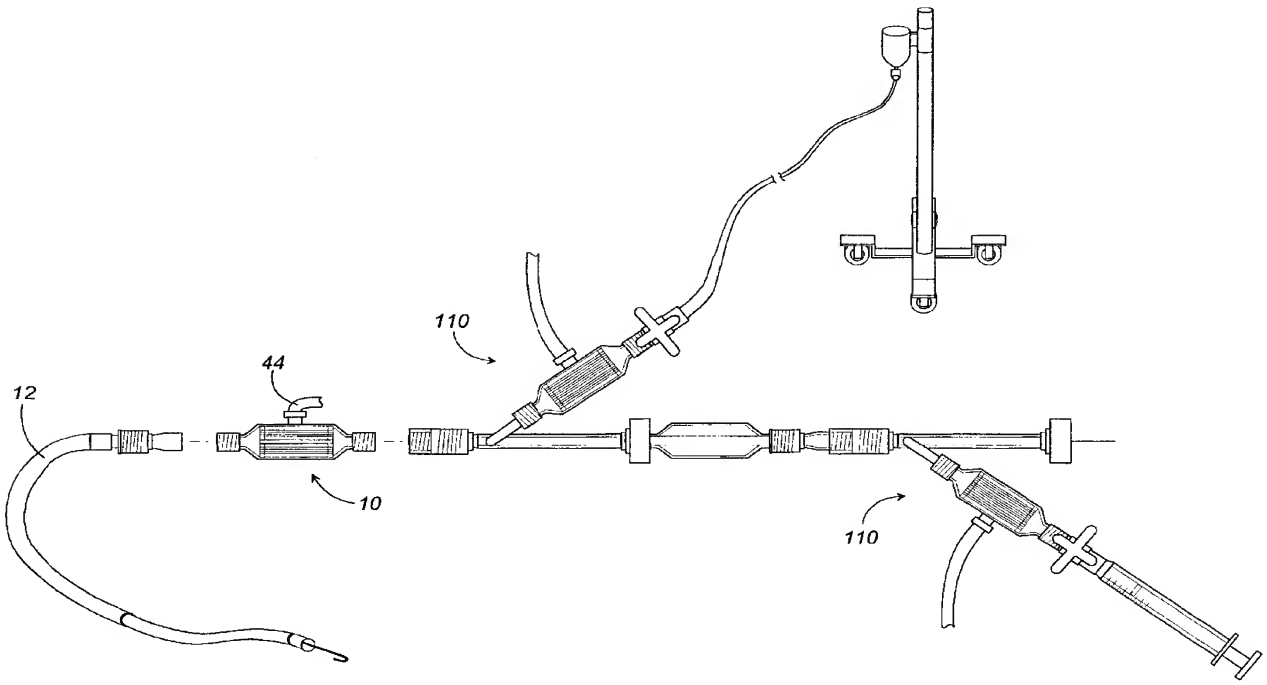
Assistant Examiner—Leonid M Fastovsky
(74) *Attorney, Agent, or Firm*—Robert H. Hammer, III

(57) **ABSTRACT**

A device **(10)** for removal of gas bubbles and dissolves gasses from fluids delivered into a patient during medical procedures is disclosed. A housing **(20)** having a number of gas permeable hollow fibers **(50)** passing therethrough is provided. The infused fluid is introduced through the interior lumens of the hollow fibers **(50)**, and entrained or dissolved gasses are drawn through the fiber walls to the outer or shell side of the fibers. A vacuum may be drawn on the housing through a vent **(32)** to enhance gas removal. A passage **(70)** is optionally provided through the device to allow a tool or other device to be passed therethrough.

27 Claims, 2 Drawing Sheets



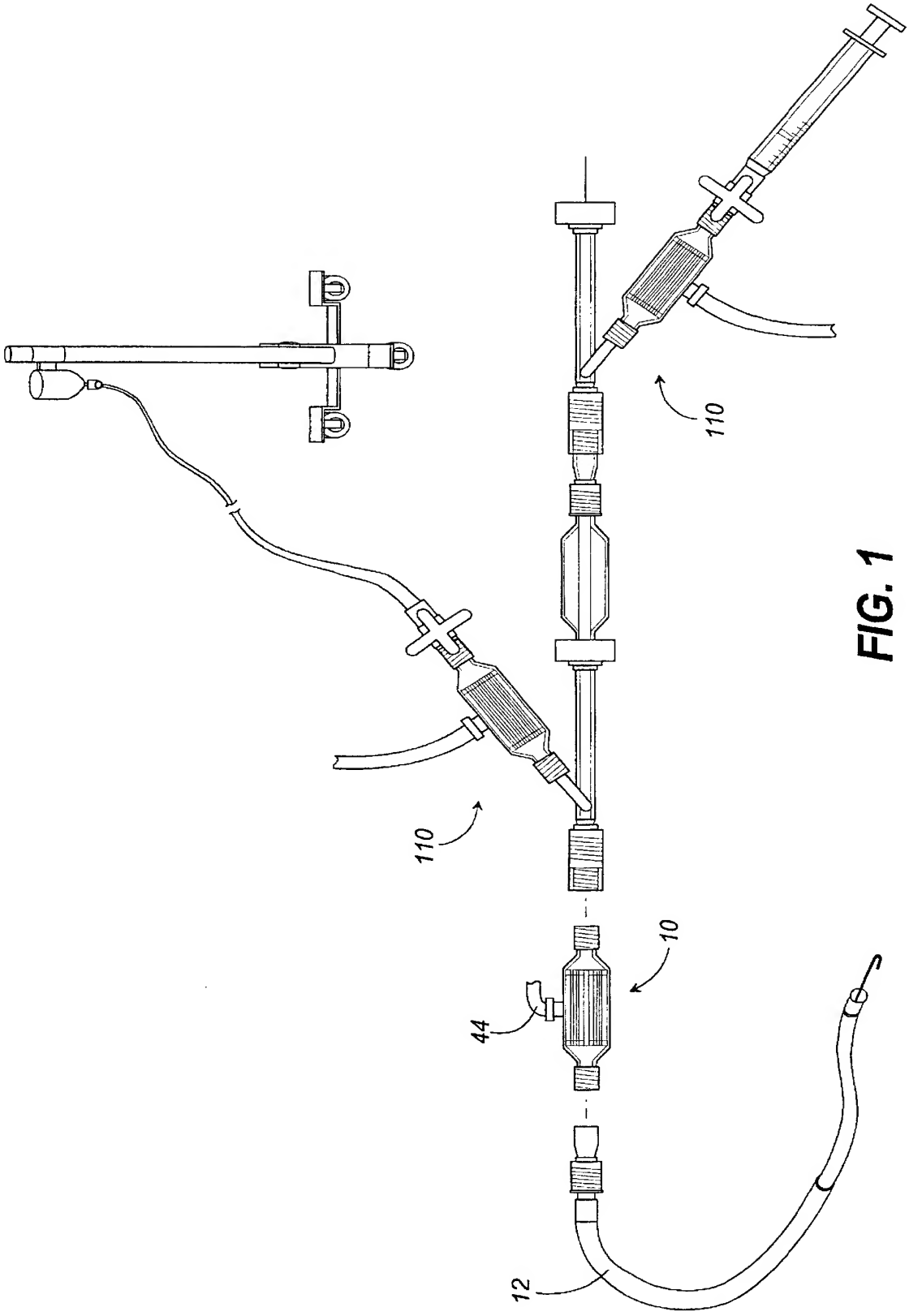
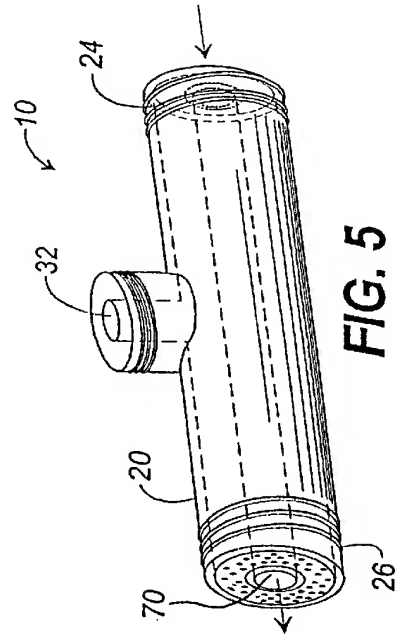


FIG. 1



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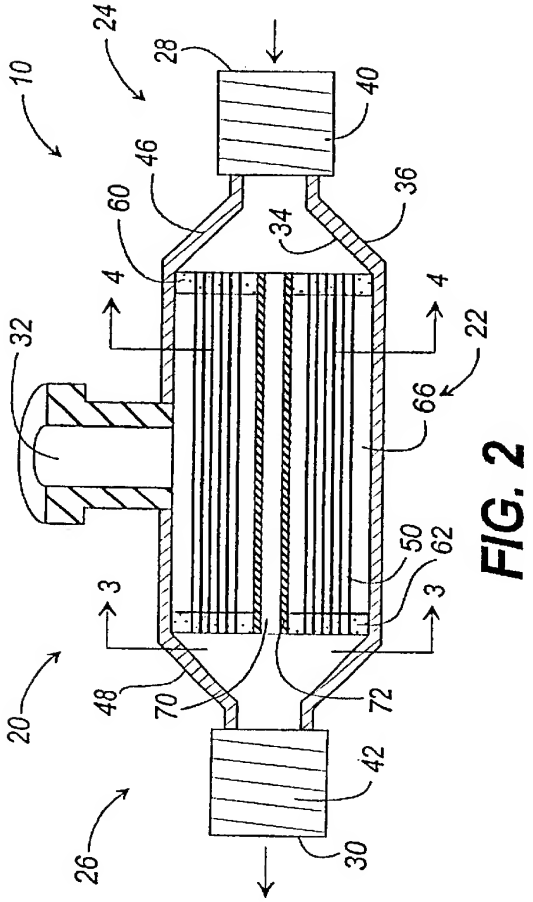

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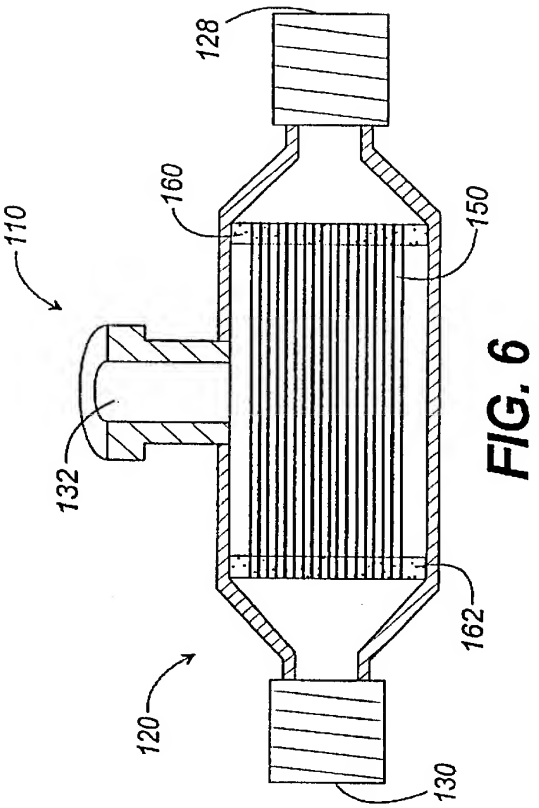

FIG. 6

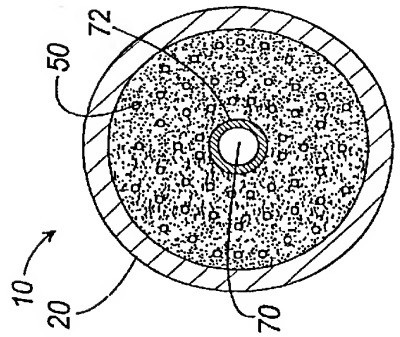

FIG. 4

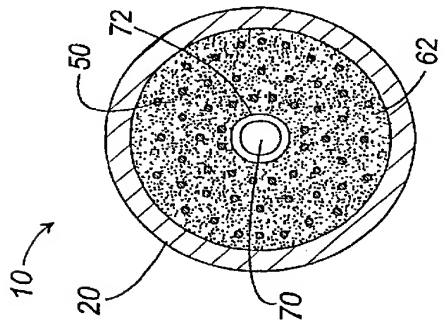

FIG. 3

DEVICE FOR REMOVAL OF GAS BUBBLES AND DISSOLVED GASSES IN LIQUID

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of Ser. No. 09/111,143 filed Jul. 7, 1998 now abandoned which claims the benefit of prior filed copending U.S. Provisional Patent Application Serial No. 60/077,892, filed Mar. 13, 1998, and of prior filed copending U.S. Provisional Patent Application Serial No. 60/068,426, filed Dec. 22, 1997. The contents of U.S. Provisional Patent Application Serial Nos. 60/077,892 and 60/068,426 are hereby incorporated herein by reference.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates generally to the medical field; and more particularly to a device for removal of gasses from fluids delivered to a patient during a medical procedure.

2. Description of Related Art

It is often desirable to introduce one or more fluids to an internal site of a patient during a medical procedure. The fluid introduced can be, for example, a drug, an anesthetic, blood, saline, flush solution, a marker dye, intravenous nutrients, or other bioactive fluids or soluble medications. Fluid delivery may be necessary or desirable in medical procedures including conventional angiography, interventional angiography, neurointerventional angiography, cardiac catheterization, arterial pressure monitoring, Swanz-Ganz catheterization, indwelling catheters, and intravenous or interarterial delivery procedures.

In order to prevent or minimize the risk of injury to the patient from air embolism, it is generally necessary to eliminate air or other gasses from the fluid delivered. Typically, fluid delivery lines are manually cleared of visible air bubbles by flushing prior to use. Existing drip chamber devices used with some fluid delivery systems to reduce the likelihood of air embolism must be maintained in an upright position to prevent the formation of air bubbles in a fluid delivery line. Thus, inadvertent tilting of the device can endanger the patient. The risk of air bubble formation increases with increasing drip rate. Dissolved gasses within the delivered fluid can form bubbles out of solution due to pressure changes, temperature changes, flow irregularities, or other factors. Thus it can be seen that a need yet exists for a gas elimination device for removing gas bubbles and/or dissolved gas from fluids delivered to an internal site of a patient during a medical procedure. A further need exists for such a device that is not required to be maintained in an upright configuration, and that permits use with standard fluid delivery equipment. A need also exists for such a device that can be located at a point in the fluid delivery line near the patient, to minimize the potential for bubble formation between the device and the patient.

It is frequently desirable to access the internal site of delivery of the fluid, as by a surgical tool, and/or monitoring equipment. previously known devices typically do not make provision for access therethrough. Thus, it can be seen that a need exists for a gas elimination device that permits access to the fluid delivery site by a surgical tool or monitoring device.

It is to the provision of a gas elimination device meeting these and other needs that the present invention is primarily directed.

SUMMARY OF THE INVENTION

Briefly described, in preferred form, one aspect of the invention is a device for removing gas bubbles and dissolved gases from fluids introduced to a patient during medical procedures. The device can be used for intravenous or intraarterial applications, including without limitation: conventional angiography, interventional angiography, neurointerventional angiography, cardiac catheterization, arterial pressure monitoring, Swanz-Ganz catheters, syringes or intravenous lines for injection of drugs or solutes or nutrients, arterial lines, venous lines, and indwelling catheters, or during operative procedures. The device preferably includes a housing having a first end comprising an inlet port, a second end comprising an outlet port, an interior surface extending between the inlet port and the outlet port, and a vent port between the inlet port and the outlet port. The device preferably further includes at least one hollow fiber membrane within the housing, each having a first end adjacent the inlet port and a second end adjacent the outlet port. A first fluid tight seal is provided between the first end of the at least one hollow fiber membrane and the interior surface of the housing. A second fluid tight seal is provided between the second end of the at least one hollow fiber membrane and the interior surface of the housing.

In another aspect, the present invention comprises a device for removal of gas from a liquid, the device comprising a housing having a fluid inlet, a fluid outlet and a gas vent; a sealed chamber within the housing between the fluid inlet and the fluid outlet, and in communication with the gas vent; and a plurality of hollow fiber membranes extending through the sealed chamber, each having a first end in communication with the fluid inlet and a second end in communication with the fluid outlet.

In another aspect, the present invention comprises a device for removal of gas from a liquid infused to an internal delivery site, and for allowing passage of a medical implement to the internal delivery site. The medical implement may be, for example, a catheter, a catheter guide wire, a probe, a laparoscope, or another surgical or monitoring instrument. The device preferably includes a housing comprising a fluid inlet, a fluid outlet and a gas vent. A sealed chamber is preferably provided within the housing between the fluid inlet and the fluid outlet. The sealed chamber is in communication with the gas vent. A plurality of hollow fiber membranes extend through the sealed chamber, each having a first end in communication with the fluid inlet and a second end in communication with the fluid outlet. A passage is provided through the sealed chamber for allowing passage of the medical implement through the device to the delivery site. The passage comprises a first end in communication with the fluid inlet, a second end in communication with the fluid outlet, and a sleeve extending between the first and second ends.

Another aspect of the present invention is a method of removing gas from a liquid infused to an internal delivery site of an organism, and accessing the internal delivery site with a medical implement. The method preferably includes passing the liquid through at least one hollow fiber membrane within a housing; degassing the liquid by removing gasses through pores in the at least one hollow fiber membrane; infusing the liquid to the internal delivery site; and accessing the internal delivery site by passing the medical implement through a passage extending through the housing.

Another aspect of the present invention is a method of fabricating a device for removal of a gas from a liquid. The

method preferably comprises providing a housing having an inlet port, an outlet port and a vent port; installing a plurality of hollow fiber membranes within the housing, extending generally from adjacent the inlet port to adjacent the outlet port; installing an annulus within the housing, extending generally from adjacent the inlet port to adjacent the outlet port; and applying first and second sealing means at the ends of the plurality of hollow fiber membranes and the ends of the annulus, to form a fluid tight seal between the plurality of hollow fiber membranes, the annulus, and the housing.

These and other features and advantages of preferred forms of the present invention are described more fully herein with reference to the accompanying drawing figures.

BRIEF DESCRIPTION OF THE DRAWING FIGURES

FIG. **1** shows preferred forms of the device of the present invention in situ in a catheter infusion system.

FIG. **2** shows a side view, in partial cross-section, of one form of the device of the present invention.

FIG. **3** shows a cross-sectional view of the device shown in FIG. **2**, taken along line **3**—**3**.

FIG. **4** shows a cross-sectional view of the device shown in FIG. **2**, taken along line **4**—**4**.

FIG. **5** shows a perspective view of another form of the device of the present invention.

FIG. **6** shows a side view, in partial cross-section, of another form of the device of the present invention.

DETAILED DESCRIPTION

FIGS. **2**–**4** show a device **10**, according to one preferred embodiment of the present invention. The device **10** can be coupled to any fluid infusion line, such as the catheter flush line **12** as shown in FIG. **1**, for removal of gas bubbles and dissolved gas from the fluid passing through the line. The device **10** includes a fluid-tight housing **20**, which is preferably fabricated from a rigid FDA grade material, such as polycarbonate, as a "T" or "Y" fitting. The housing **20** generally comprises a body portion **22**, and first and second ends **24**, **26**. First end **24** comprises an inlet port **28** for receiving a liquid, and second end **26** comprises an outlet port **30** for discharging the degassed liquid for delivery to an internal delivery site of a patient. A vacuum or vent port **32** is also provided in the housing between the inlet **28** and the outlet **30**. The housing **20** further comprises an interior surface **34** and an exterior surface **36** extending between first and second ends **24**, **26**. First and second endcaps **40**, **42** can be provided at first and second ends **24**, **26** of the housing, and can be provided with detachable couplings for coupling the device **10** to the line **12**. The endcaps **40**, **42** can be integrally formed with the body portion **22** of the housing **20**, as by injection molding or other known fabrication methods; or can be separately formed and attached to the body portion **22** by solvent welding, ultrasonic welding, thermal welding, adhesives, or other attachment means. The detachable couplings can comprise threaded, compression, twist-lock, or other fittings. In a preferred embodiment, Luer lock quick-connect fittings are provided at the first and second ends of the housing **20**. The vacuum or vent port **32** can also be provided with a quick-connect fitting, threads or other detachable coupling means for connection to an external vacuum source through a vacuum line **44** (FIG. **1**). The housing **20** can take any of a number of physical configurations, including the cylindrical housing with reduced diameter neck portions **46**, **48** at its first and second ends **24**, **26** shown in FIGS. **1** and **2**, and the straight-walled cylinder configuration shown in FIG. **5**. The housing **20** can be a commercially-available "T" or "Y" fitting, or can be specially fabricated for the particular application involved. In the alternate design shown in FIG. **5**, the housing is formed as a single cylindrical piece, with generally straight walls having detachable couplings formed at each end thereof.

At least one, and preferably a plurality of hollow fiber membranes **50** extend generally axially through the housing **20**, from adjacent the first end **24** to adjacent the second end **26**. Each fiber extends between a first end adjacent the inlet **28** and a second end adjacent the outlet **30**. The fibers **50** can be a microporous hydrophobic hollow fiber membrane, such as are available commercially as polyolefin membranes. Example materials include: polypropylene, polyethylene, or polymethylpentene. The fibers **50** typically have an outside diameter of approximately 200–400 microns, a wall thickness of approximately 25–50 microns, a pore size of between approximately 0.01 to 0.2 microns (sufficiently small to prevent fluid breakthrough), and a porosity of approximately 10–50% (sufficiently high to provide adequate flux of gas and gas bubble passage from the aqueous fluid in the internal lumens of the fibers **50** to the gas phase exterior of the fibers **50**). The fiber membranes **50** are constructed of suitable FDA grade materials. A porous hydrophobic membrane allows for direct removal of bubbles from aqueous fluids without liquid penetration into the pores according to the Young-Laplace formula. Removal of dissolved gasses present in the liquid can be additionally facilitated by use of vacuum on the shell side of the device, through the vacuum or vent port **32**, due to partial pressure difference of the gasses in the liquid and gas phases according to Henry's Law.

Although microporous hydrophobic hollow fiber membranes are described above, any porous hollow fiber material, whether hydrophobic or hydrophilic, can be used to form the fibers **50**, with the application of a thin coating or skin of a polymer having suitable permeability to the dissolved gasses (for example, oxygen, nitrogen, carbon dioxide) in the aqueous fluid passed through the tubing **12**, but rendering the pores of the fibers **50** impermeable to passage of the aqueous fluid therethrough. Example polymer coatings include silicones, polymethylpentene, and other FDA grade polymers. The polymer skin is preferably applied to the liquid surface (the internal lumen surface) of the hollow fiber **50**, to prevent liquid penetration into the pores. Vacuum applied to the shell side of the device **10** through the vent **32** facilitates removal of dissolved gasses from the liquid. Although the polymer skin typically prevents direct removal of bubbles present in the liquid, entrained bubbles in the liquid will dissolve into the liquid once sufficient dissolved gasses are removed from the liquid. Once dissolved, the gasses can be removed from the liquid.

The fiber membranes **50** are held in place at their first and second ends within the housing **20** by first and second fluid tight seals **60**, **62**. The first and second seals **60**, **62** can comprise, for example, a potting resin that fills the voids between the fibers **50**, and bonds to the interior surface **34** of the housing **20** to form a fluid tight seal once hardened or cured. The potting resin can comprise, for example, a multicomponent (resin and hardener component) thermosetting or UV-curable FDA grade resin, such as for example, silicone, urethane or epoxy, all of which will provide secure attachment of the fibers **50** within the housing **20**, as well as insuring a fluid tight seal around the fibers **50** and against the interior surface **34**. As seen best in the cross-sectional view

of FIG. **3**, the fluid tight seals **60**, **62** (seal **62** is depicted in FIG. **3**) are closely formed around the external surfaces of the fibers **50** and, if present, the sleeve **72**, which is more fully described below. As seen best in the cross-sectional view of FIG. **4**, the fibers **50** and, if present, the sleeve **72** extend freely between the first and second fluid tight seals **60**, **62**. Alternatively, intermediate supports and/or baffles can be provided between the first and second fluid tight seals **60**, **62**. The first and second fluid tight seals **60**, **62**, along with the interior surface **34** of the housing **20**, define a sealed chamber **66** within the housing **20**. The sealed chamber **66** is in communication with the vent **32**, thereby allowing gasses within the chamber **66** to be exhausted, and allowing a vacuum to be applied to the chamber **66** through the vent **32**. As seen best in FIG. **2**, the sealed chamber **66** is arranged between the inlet **28** and the outlet **30**, and the hollow fiber membranes **50** extend through the chamber **66**. The first ends of the fibers **50** are in communication with the fluid inlet **28**, and the second ends of the fibers **50** are in communication with the fluid outlet **30**. In this manner, any fluids transferred from the inlet **28** to the outlet **30** must pass through the interior lumens of the fibers **50**.

In its more preferred forms, the invention further comprises one or more passages **70**, extending through the sealed chamber **66**, and having first and second ends extending through the first and second fluid tight seals **60**, **62**. The passage **70** allows an implement such as a surgical tool or instrument to pass through the device **10** and access the internal site of fluid delivery. For ease of access, the first end of the passage **70** is preferably generally aligned with and in communication with the inlet **28**, and the second end of the passage **70** is generally aligned with and in communication with the outlet **30**. Although one passage **70** is depicted, multiple passages may be provided. For example one passage may be provided for access by a surgical tool, and another passage may be provided for access by a monitoring device such as a fiberoptic endoscope. The passage **70** preferably comprises a generally tubular sleeve **72** extending generally axially through the center of the interior of the housing **20**. Each end of the sleeve **72** is held in place, and a fluid tight seal is formed around the exterior surfaces thereof, by the first and second fluid tight seals **60**, **62**. The sleeve **72** is preferably constructed of a suitable FDA grade polymeric material such as polycarbonate, polypropylene or polyethylene. Tool sealing means can be provided, for example, by selecting the inner diameter of the sleeve **72** to generally match the outer diameter of the tool or device intended to be inserted therethrough, so as to slidingly engage the tool and form a seal against fluid passage through the passage **70** between the sleeve **72** and the tool. Alternatively, the tool sealing means can comprise a separate tool-sealing element, such as a flexible rubber or plastic lip, gasket or O-ring provided in the passage **70**. Although the passage **70** has been described as tubular, it may have a cross-sectional geometry other than circular, as required to match the outer geometry of the tool or device to be passed therethrough. Closure means can also be provided for maintaining the passage **70** closed to fluid passage when the tool is not installed therethrough. The closure means and the tool sealing means can comprise the same or different components. For example, the sleeve **72** can be formed from a resilient, flexible material, which will stretch to permit passage of the tool or device and automatically create a sealing engagement with the outer surface thereof, regardless of its shape, and contract to close the passage **70** when the tool is not installed therethrough. Alternatively, a flap, iris, spring mechanism, elastic band, or other closure means, biased to closure against fluid passage but openable upon insertion of a tool or other device, can be provided within the passage **70** or adjacent the sleeve **72**.

FIG. **6** shows another preferred form of the present invention. This embodiment of the device **110** can be generally similar to the devices described herein with reference to FIGS. **2–5**, with the exception of the absence of the tubular sleeve **72** that forms the passage **70**. As shown in FIG. **1**, the device **110** can be used in sections of the fluid delivery system wherein passage of a tool or other device is not required, for example, for gas removal from a fluid line between an intravenous drip bag or a syringe and the flush line **12**. The device **110** preferably includes a housing **120**, an inlet **128**, an outlet **130**, and a vent **132**. A plurality of hollow fiber membranes **150** preferably extend between first and second fluid tight seals **160**, **162**. Fluid is passed from the inlet **128** to the outlet **130** through the hollow fiber membranes **150**, and bubbles and/or dissolved gasses are removed from the fluid through the hollow fiber membranes **150** and discharged through the vent **132**. If desired, a vacuum can be applied to the vent **132** to enhance gas removal.

Methods of fabrication and use of the device of the present invention will now be described. Although these methods are described with reference to the embodiment of the device **10** depicted by FIGS. **2–5**, it will be understood that other embodiments, such as for example the device **110** depicted by FIG. **6**, can be fabricated and used according to similar methods, with the omission of the sleeve **72** and the passage of a tool or other device through the passage **70**. The device **10** can be fabricated by inserting the hollow fibers **50** and the sleeve **72** through the housing **20**, extending from adjacent the inlet port **28** to adjacent the outlet port **30**. The fibers **50** and the sleeve **72** preferably initially extend somewhat beyond the housing ends, and/or are sealed at their ends to prevent ingress of potting resin into the interior lumens thereof during construction. The first and second fluid tight seals **60**, **62** are then formed around the fibers **50** and the sleeve **72** by applying a seal forming material such as potting resin across the interior surface **34** of the housing **20** adjacent the first and second ends **24**, **26**. The seal forming material fills the spaces between the fibers **50** and the sleeve **72**, and bonds to the interior surface **34** of the housing **20**, thereby forming the fluid-tight seals and isolating the sealed chamber **66** from the inlet **28** and the outlet **30**. The potting resin is cured or allowed to harden. The ends of the fibers **50** and the sleeve **72** are cut approximately flush with the outer surfaces of the first and second fluid tight seals **60**, **62**, thereby exposing the open ends of the lumens of the fibers **50** and the sleeve **72**.

The device **10** of the present invention is utilized by installing the device **10** in a fluid infusion line, such as the catheter flush line **12** as shown in FIG. **1**. The outlet port **30** of the housing **20** is connected, preferably by means of quick connect fittings, to an end of the catheter line **12**. The inlet port **28** of the housing **20** is connected to an infusion and access system, which may include one or more fluid delivery means such as the two depicted syringe and flush solution line arrangements, and one or more access points such as the depicted guide wire insertion point. In many applications, it will be desirable to install the device as close to the fluid delivery site as possible, in order to minimize the potential for bubble formation between the device and the fluid delivery site. An external vacuum source may be connected to the vacuum port **32** of the housing **20**, through the vacuum line **44**, to apply a negative relative pressure to the shell side of the device **10** to assist in drawing gasses out of the liquid

through the walls of the fibers **50**. Fluids may then be infused from the fluid delivery means, through the lumens of the fibers **50**, and through the infusion line **12**. As the fluids pass through the lumens of the fibers **50**, gas bubbles and/or dissolved gasses in the fluids are removed from the fluids through the pores of the fibers **50**, and out the vent or vacuum port **32** in the housing **20**. Because liquids do not pass through the pores in the fibers **50**, the gas-stripped liquid continues through the lumens of the fibers **50**. A tool or other device, such as the depicted catheter guide wire, can be inserted into the guide wire insertion point, passed through the passage **70**, and through the catheter line **12**. The outer geometry of the device preferably fits in close engagement with the inner diameter of the sleeve **72** to act as a seal against fluid passage. In addition to the depicted guide wire, a variety of devices may be inserted through the system as described. For example, a fiberoptic endoscope may be inserted to view internal tissue, and/or surgical instruments may be inserted to carry out any of a number of surgical procedures.

While the invention has been described in its preferred forms, it will be readily apparent to those of ordinary skill in the art that many additions, modifications and deletions can be made thereto without departing from the spirit and scope of the invention.

What is claimed is:

1. A device for removal of gas from a liquid in a medical fluid infusion line, said device comprising:

(a) a housing having a first end comprising an inlet port, a second end comprising an outlet port, an interior surface extending between said inlet port and said outlet port, and a vacuum port between said inlet port and said outlet port;

(b) a plurality of hollow fiber membranes within said housing, each said hollow fiber membrane having a first end adjacent the inlet port and a second end adjacent the outlet port;

(c) a first fluid tight seal between the first end of each said hollow fiber membrane and the interior surface of the housing; and

(d) a second fluid tight seal between the second end of each said hollow fiber membrane and the interior surface of the housing.

2. The device of claim **1**, wherein each said hollow fiber membrane comprises a microporous hydrophobic material.

3. The device of claim **2**, wherein said microporous hydrophobic material comprises a polyolefin.

4. The device of claim **3**, wherein said polyolefin comprises polypropylene.

5. The device of claim **3**, wherein said polyolefin comprises polyethylene.

6. The device of claim **3**, wherein said polyolefin comprises polymethylpentene.

7. The device of claim **1**, wherein each said hollow fiber membrane comprises a hollow fiber microtubing with a gas permeable coating.

8. The device of claim **7**, wherein said gas permeable coating comprises silicon.

9. The device of claim **7**, wherein said gas permeable coating comprises polymethylpentene.

10. The device of claim **7**, wherein said gas permeable coating is applied to an internal lumen of said hollow fiber microtubing.

11. The device of claim **1**, wherein each said hollow fiber membrane comprises a material having a porosity of approximately 10–50%.

12. The device of claim **11**, wherein said material comprises a plurality of pores having a pore size of approximately 0.01 to 0.2 microns.

13. The device of claim **1**, wherein said first and second fluid tight seals comprise a potting resin selected from the group consisting of thermosetting resins, UV-curable resins, silicone, urethane and epoxy.

14. The device of claim **1**, wherein said inlet port and said outlet port comprise detachable couplings for releasably engaging fluid delivery conduit.

15. The device of claim **1**, wherein said vacuum port comprises a detachable coupling for releasably engaging a vacuum line.

16. The device of claim **1**, further comprising a sealed passage extending through said first and second fluid tight seals.

17. The device of claim **16**, wherein said sealed passage comprises a sleeve having a first end generally aligned with said inlet port of said housing and a second end generally aligned with said outlet port of said housing.

18. The device of claim **17**, further comprising tool sealing means for slidably engaging a tool received in said sleeve.

19. The device of claim **16**, further comprising closure means for maintaining said sealed passage closed to fluid passage.

20. The device of claim **16**, wherein said sealed passage comprises a resilient flexible material.

21. A device for removal of gas from a liquid in a medical fluid infusion line, said device comprising:

(a) a housing comprising a fluid inlet, a fluid outlet and a vacuum vent;

(b) a sealed chamber within said housing between said fluid inlet and said fluid outlet, said sealed chamber being in communication with said vacuum vent; and

(c) a plurality of hollow fiber membranes extending through said sealed chamber, each of said plurality of hollow fiber membranes having a first end in communication with said fluid inlet and a second end in communication with said fluid outlet.

22. The device of claim **21**, wherein said plurality of hollow fiber membranes comprise a microporous hydrophobic material.

23. The device of claim **21**, wherein said plurality of hollow fiber membranes comprise porous hollow fiber microtubes having a gas permeable coating.

24. The device of claim **21**, wherein said housing comprises a first endcap adjacent said fluid inlet, and a second endcap adjacent said fluid outlet, and wherein said first and second endcaps and said vacuum vent comprise detachable couplings.

25. The device of claim **21**, further comprising a passage through said sealed chamber, said passage comprising a first end in communication with said fluid inlet, a second end in communication with said fluid outlet, and a sleeve extending between said first and second ends.

26. A device for removal of gas from a liquid infused to an internal delivery site, and for allowing passage of a medical implement to the internal delivery site, said device comprising:

(a) a housing comprising a fluid inlet, a fluid outlet and a vacuum vent;

(b) a sealed chamber within said housing between said fluid inlet and said fluid outlet, said sealed chamber being in communication with said vacuum vent;

(c) a plurality of hollow fiber membranes extending through said sealed chamber, each of said plurality of hollow fiber membranes having a first end in communication with said fluid inlet and a second end in communication with said fluid outlet; and

(d) a passage through said sealed chamber, said passage comprising a first end in communication with said fluid inlet, a second end in communication with said fluid outlet, and a sleeve extending between said first and second ends.

27. A method of removing gas from a liquid infused to an internal delivery site of an organism, and accessing the internal delivery site with a medical implement, the method comprising:

(a) passing the liquid through at least one hollow fiber membrane within a housing;

(b) degassing the liquid by removing gasses through pores in the at least one hollow fiber membrane;

(c) infusing the liquid to the internal delivery site; and

(d) accessing the internal delivery site by passing the medical implement through a passage extending through the housing.

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